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(54) Title: FUSED-RING ARYL SUBSTITUTED IMIDAZOLES

(I)

(57) Abstract

Substituted imidazoles of formula (I) are useful as angiotensin II blockers. These compounds have activity in treating hypertension and congestive heart failure.

* See back of page

DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

TITLE
FUSED-RING ARYL SUBSTITUTED IMIDAZOLES
Related Application

This is a continuation-in-part of USSN 07/375,069 filed June 30, 1989. Also, Carini, Duncia and Wong U.S. application Serial No. 07/279,194, filed December 6, 1988, discloses and claims substituted imidazoles which are angiotensin II (AII) blockers and their use, alone or in combination with other drugs, to treat hypertension and congestive heart failure.

BACKGROUND OF THE INVENTION
Field of the Invention

This invention relates to novel substituted imidazoles, and processes for their preparation. The invention also relates to pharmaceutical compositions containing the novel imidazoles and pharmaceutical methods using them, alone and in conjunction with other drugs, especially diuretics and non-steroidal anti-inflammatory drugs (NSAID's).

The compounds of this invention inhibit the action of the hormone angiotensin II (AII) and are useful therefore in alleviating angiotensin induced hypertension. The enzyme renin acts on a blood plasma α_2-globulin, angiotensinogen, to produce angiotensin I, which is then converted by angiotensin converting-enzyme to AII. The latter substance is a powerful vasopressor agent which has been implicated as a causitive agent for producing high blood pressure in various mammalian species, such as the rat, dog, and man. The compounds of this invention inhibit the action of AII at its receptors on target cells and thus prevent the increase in blood pressure produced by this hormone-receptor interaction. By administering a compound of this invention to a species of mammal with hypertension due

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to AII, the blood pressure is reduced. The compounds of
this invention are also useful for the treatment of
congestive heart failure. Administration of a compound
of this invention with a diuretic such as furosemide or
5   hydrochlorothiazide, either as a stepwise combined
therapy (diuretic first) or as a physical mixture,
enhances the antihypertensive effect of the compound.
Administration of a compound of this invention with a
non-steroidal anti-inflammatory drug (NSAID) can prevent
10   renal failure which sometimes results from
administration of a NSAID.

European Published Application 0 253 310, published
January 20, 1988, discloses that certain substituted
imidazoles block the AII receptor and are useful
15   therefore in alleviating angiotensin induced
hypertension as well as in treating congestive heart
failure. The imidazoles disclosed have the formula:
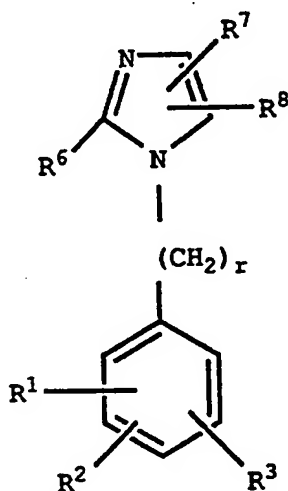
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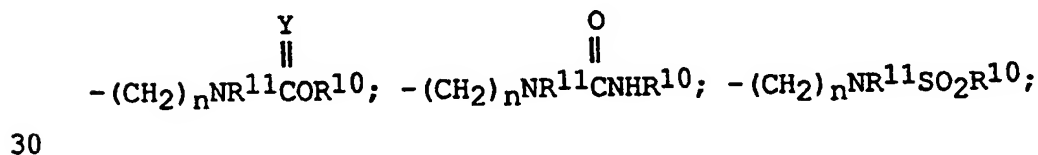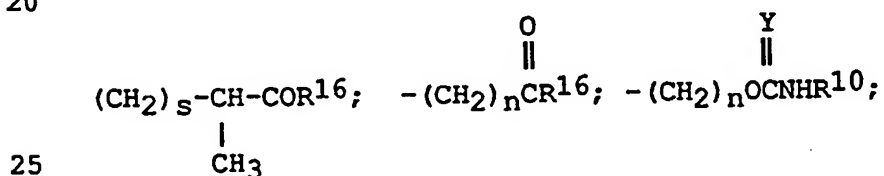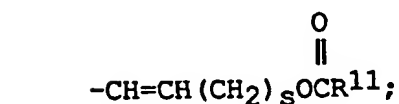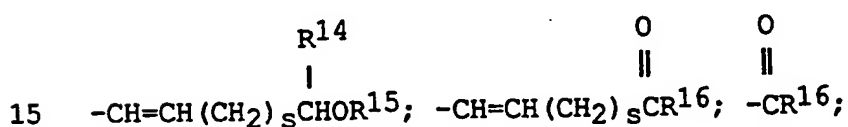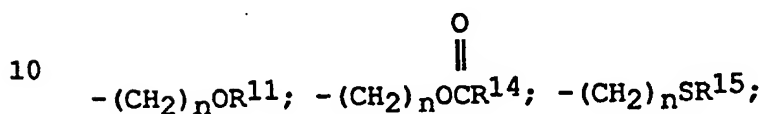The imidazoles of the present invention differ from
those of EPA 0 253 310 in the substituents R^7 and R^8 at
positions 4 and 5 of the imidazole ring. In EPA
0 253 310, R^7 and R^8 are defined as follows:
25   R^7 is H, F, Cl, Br, I, NO_2, CF_3 or CN;

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R^8 is H, CN, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, or the same groups substituted with F; phenylalkenyl wherein the aliphatic portion is 2 to 6 carbon atoms; $-(CH_2)_m$-imidazol-1-yl; $-(CH_2)_m$-1,2,3-triazolyl optionally substituted with one or two groups selected from CO_2CH_3 or alkyl of 1 to 4 carbon atoms; $-(CH_2)_m$-tetrazolyl;

$$-(CH_2)_nOR^{11}; \quad -(CH_2)_n\overset{\displaystyle O}{\overset{\displaystyle \|}{O}}CR^{14}; \quad -(CH_2)_nSR^{15};$$

$$-CH=CH(CH_2)_s\overset{\displaystyle R^{14}}{\overset{\displaystyle |}{C}}HOR^{15}; \quad -CH=CH(CH_2)_s\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16}; \quad -\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16};$$

$$-CH=CH(CH_2)_s\overset{\displaystyle O}{\overset{\displaystyle \|}{O}}CR^{11};$$

$$(CH_2)_s-\overset{\displaystyle |}{\underset{\displaystyle CH_3}{C}}H-COR^{16}; \quad -(CH_2)_n\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16}; \quad -(CH_2)_n\overset{\displaystyle Y}{\overset{\displaystyle \|}{O}}CNHR^{10};$$

$$-(CH_2)_nNR^{11}\overset{\displaystyle Y}{\overset{\displaystyle \|}{C}}OR^{10}; \quad -(CH_2)_nNR^{11}\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}NHR^{10}; \quad -(CH_2)_nNR^{11}SO_2R^{10};$$

$$-(CH_2)_nNR^{11}\overset{\displaystyle Y}{\overset{\displaystyle \|}{C}}R^{10};$$ etc., where R^{10}, R^{11}, R^{14}, R^{15}, R^{16}, and Y are as defined below for the present invention.

Pals et al., *Circulation Research*, **29**, 673 (1971) describe the introduction of a sarcosine residue in position 1 and alanine in position 8 of the endogenous vasoconstrictor hormone AII to yield an (octa)peptide that blocks the effects of AII on the blood pressure of

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pithed rats. This analog, [Sar^1, Ala^8] AII, initially
called "P-113" and subsequently "Saralasin", was found
to be one of the most potent competitive antagonists of
the actions of AII, although, like most of the so-called
5   peptide-AII-antagonists, it also possesses agonistic
actions of its own. Saralasin has been demonstrated to
lower arterial pressure in mammals and man when the
(elevated) pressure is dependent on circulating AII
(Pals et al., Circulation Research, 29, 673 (1971);
10   Streeten and Anderson, Handbook of Hypertension, Vol. 5,
Clinical Pharmacology of Antihypertensive Drugs, A. E.
Doyle (Editor), Elsevier Science Publishers B.V., p. 246
(1984)). However, due to its agonistic character,
saralasin generally elicits pressor effects when the
15   pressure is not sustained by AII. Being a peptide, the
pharmacological effects to saralasin are relatively
short-lasting and are only manifest after parenteral
administration, oral doses being ineffective. Although
the therapeutic uses of peptide AII-blockers, like
20   saralasin, are severely limited due to their oral
ineffectiveness and short duration of action, their
major utility is as a pharmaceutical standard.
        Some known non-peptide antihypertensive agents act
by inhibiting an enzyme, called angiotensin converting
25   enzyme (ACE), which is responsible for conversion of
angiotensin I to AII. Such agents are thus referred to
as ACE inhibitors, or converting enzyme inhibitors
(CEI's). Captopril and enalapril are commercially
available CEI's. Based on experimental and clinical
30   evidence, about 40% of hypertensive patients are non-
responsive to treatment with CEI's. But when a diuretic
such as furosemide or hydrochlorothiazide is given
together with a CEI, the blood pressure of the majority
of hypertensive patients is effectively normalized.
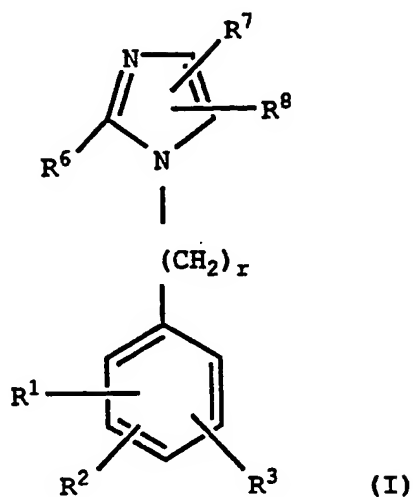35   Diuretic treatment converts the non-renin dependent

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state in regulating blood pressure to a renin-dependent
state. Although the imidazoles of this invention act by
a different mechanism, i.e., by blocking the AII
receptor rather than by inhibiting the angiotensin
5 converting enzyme, both mechanisms involve interference
with the renin-angiotensin cascade. A combination of
the CEI enalapril maleate and the diuretic
hydrochlorothiazide is commercially available under the
trademark Vaseretic® from Merck & Co. Publications
10 which relate to the use of diuretics with CEI's to treat
hypertension, in either a diuretic-first, stepwise
approach or in physical combination, include Keeton, T.
K. and Campbell, W. B., Pharmacol. Rev., 31:81 (1981)
and Weinberger, M. H., Medical Clinics N. America,
15 71:979 (1987). Diuretics have also been administered in
combination with saralasin to enhance the
antihypertensive effect.

         Non-steroidal anti-inflammatory drugs (NSAID's)
have been reported to induce renal failure in patients
20 with renal underperfusion and high plasma level of AII.
(Dunn, M.J., Hospital Practice, 19:99, 1984).
Administration of an AII blocking compound of this
invention in combination with an NSAID (either stepwise
or in physical combination) can prevent such renal
25 failure. Saralasin has been shown to inhibit the renal
vasoconstrictor effect of indomethacin and meclofenamate
in dogs (Satoh et al., Circ. Res. 36/37 (Suppl. I):I-89,
1975; Blasingham et al., Am. J. Physiol. 239:F360,
1980). The CEI captopril has been demonstrated to
30 reverse the renal vasoconstrictor effect of indomethacin
in dogs with non-hypotensive hemorrhage. (Wong et al.,
J. Pharmacol. Exp. Ther. 219:104, 1980).
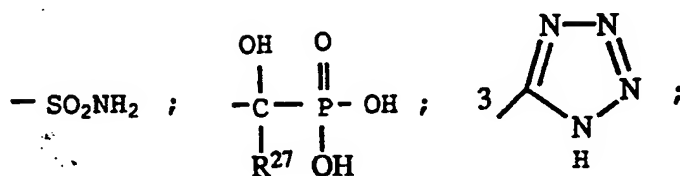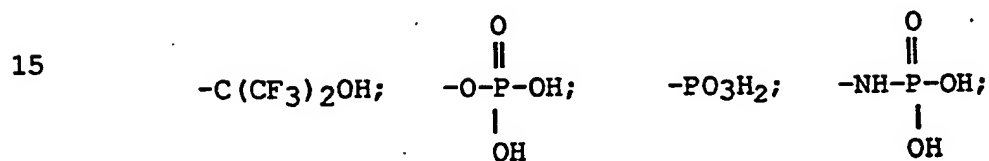
                    Summary Of The Invention

         According to the present invention there are
35 provided novel compounds of formula (I) which have

angiotensin II-antagonizing properties and are useful as antihypertensives.

(I)

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wherein

10 R^1 is 4-CO_2H; 4-CO_2R^9;

$$-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-OH;$$

-SO_3H;

15 -$C(CF_3)_2OH$;

$$-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH;$$

-PO_3H_2;

$$-NH-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH;$$

20 4-$NHSO_2CH_3$; 4-$NHSO_2CF_3$; -$CONHOR^{12}$;

-SO_2NH_2 ;

$$-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle R^{27}}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}-OH ;$$

; 4-CONHNHSO$_2$CF$_3$; 4-COHN-CHCH$_2$C$_6$H$_5$;

(*ℓ*-isomer)

(*ℓ*-isomer);

or

R^{2}is H; Cl; Br; I; F; NO$_2$; CN; alkyl of 1 to 4 carbon
atoms; acyloxy of 1 to 4 carbon atoms; alkoxy of
1 to 4 carbon atoms; CO$_2$H; CO$_2$R^9; NHSO$_2$CH$_3$;
NHSO$_2$CF$_3$;

$CONHOR^{12}$; SO_2NH_2;

R³ is H; Cl, Br, I or F; alkyl of 1 to 4 carbon atoms or
       alkoxy of 1 to 4 carbon atoms;

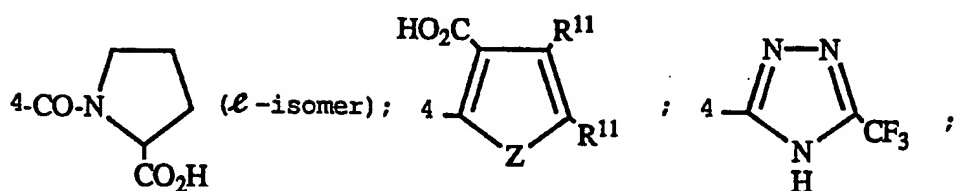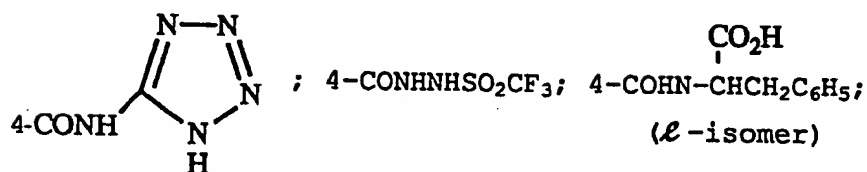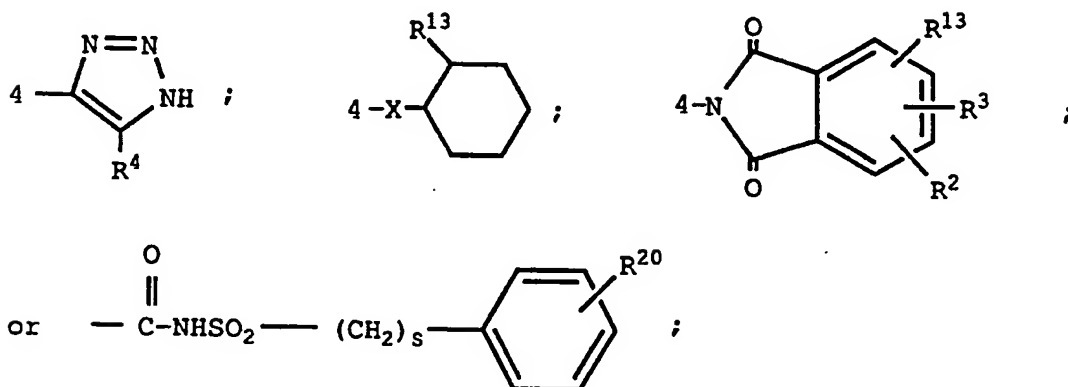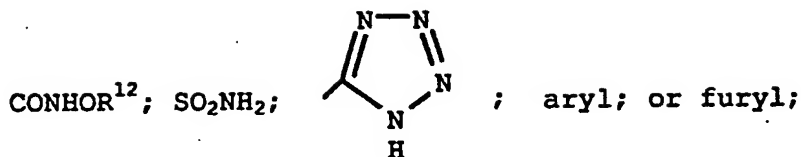R⁴ is CN, NO_2 or CO_2R^{11};

R⁵ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3
       to 6 carbon atoms, alkenyl or alkynyl of 2 to 4
       carbon atoms;

R⁶ is alkyl of 2 to 10 carbon atoms, alkenyl or alkynyl
       of 3 to 10 carbon atoms or the same groups
       substituted with F or CO_2R^{14}; cycloalkyl of 3 to 8
       carbon atoms, cycloalkylalkyl of 4 to 10 carbon
       atoms; cycloalkylalkenyl or cycloalkylalkynyl of 5
       to 10 carbon atoms; $(CH_2)_sZ(CH_2)_mR^5$ optionally
       substituted with F or CO_2R^{14}; benzyl or benzyl
       substituted on the phenyl ring with 1 or 2
       halogens, alkoxy of 1 to 4 carbon atoms, alkyl of 1
       to 4 carbon atoms or nitro;

R⁷ is 1- or 2-naphthyl; 5- or 6-naphthoquinonyl; 3-, 4-
       or 5-acenaphthyl; 3-, 4- or 5-acenaphthenyl; 1-,
       2- or 9-anthracenyl; 1- or 2-anthraquinonyl; 1-,
       2-, 3-, 4-, or 9-phenanthrenyl; 2-, 3-, 4-, 5-,
       6-, 7- or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7- or
       8-isoquinolinyl; 2-, 3-, 4-, 5-, 6- or 7-indolyl
       which can be substituted on ring nitrogen with
       lower alkyl of 1 to 5 carbon atoms or benzyl; 4-,
       5-, 6- or 7-indenyl; 2-, 3-, 4-, 5-, 6- or 7-
       benzofuryl; 2-, 3-, 4-, 5-, 6- or 7-benzothienyl;
       1-, 2-, 3- or 4-dibenzofuryl; 1-, 2-, 3- or 4-
       dibenzothienyl; 1-, 2-, 3- or 4-fluorenyl; any of
       the foregoing polycyclic aryl groups substituted

with 1 or 2 substituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, $-NO_2$, $-CN$, $-CF_3$, $-COR^{16}$, $-CH_2OR^{17}$, $-NHCOR^{17}$, $-CONR^{18}R^{19}$, $S(O)_rR^{17}$, and $SO_2NR^{18}R^{19}$;

5   the anhydride of 4, 5-dicarboxyl-1- or 2-naphthyl; or substituted alkyl of 1 to 10 carbon atoms, alkenyl or alkynyl of 2 to 10 carbon atoms substituted with a substituted or unsubstituted polycyclic aryl group as defined above;

10      $-S(O)_r$-heteroaryl; $-NR^{18}$-heteroaryl, and $-NH-SO_2$-heteroaryl;

15   R^8 is $-(CH_2)_{n-1}\underset{\overset{|}{OR^{17}}}{CH}-R^{11}$; $-(CH_2)_n\overset{\overset{O}{\|}}{O}CR^{14}$; $-(CH_2)_nSR^{15}$;

20      $-CH=CH(CH_2)_s\underset{\overset{|}{R^{14}}}{CH}OR^{15}$; $-CH=CH(CH_2)_s\overset{\overset{O}{\|}}{C}R^{16}$; $-\overset{\overset{O}{\|}}{C}R^{16}$;

25      $-CH=CH(CH_2)_s\overset{\overset{O}{\|}}{O}CR^{11}$; $-(CH_2)_m$-tetrazolyl;

30      $(CH_2)_s\underset{\overset{|}{CH_3}}{CH}-COR^{16}$; $-(CH_2)_n\overset{\overset{O}{\|}}{C}R^{16}$; $-(CH_2)_n\overset{\overset{Y}{\|}}{O}CNHR^{10}$;

35      $-(CH_2)_nNR^{11}\overset{\overset{Y}{\|}}{C}OR^{10}$; $-(CH_2)_nNR^{11}\overset{\overset{O}{\|}}{C}NHR^{10}$; $-(CH_2)_nNR^{11}SO_2R^{10}$;

     $-(CH_2)_nNR^{11}\overset{\overset{Y}{\|}}{C}R^{10}$;

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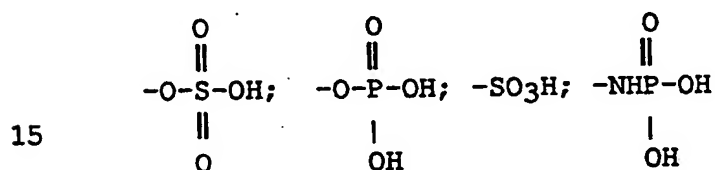R^9 is $-\overset{R^{24}}{\underset{|}{CH}}-O\overset{O}{\underset{||}{C}}R^{21}$;

R^{10} is alkyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl, 1-naphthyl, 1-(1-naphthyl)ethyl, or $(CH_2)_pC_6H_5$;
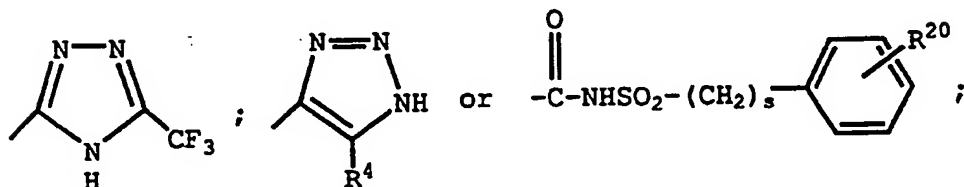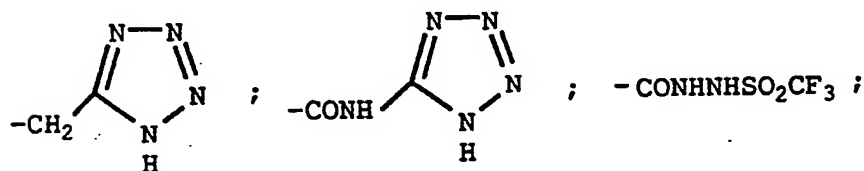
R^{11} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{12} is H, methyl or benzyl;

R^{13} is $-CO_2H$; $-CO_2R^9$; $-CH_2CO_2H$, $-CH_2CO_2R^9$;

$$-O-\overset{O}{\underset{||}{\underset{||}{S}}}-OH; \quad -O-\overset{O}{\underset{|}{\underset{OH}{P}}}-OH; \quad -SO_3H; \quad -NH\overset{O}{\underset{|}{\underset{OH}{P}}}-OH$$

$-PO_3H_2$; $-C(CF_3)_2OH$; $-NHSO_2CH_3$; $-NHSO_2CF_3$; $-NHCOCF_3$;

$-CONHOR^{12}$; $-SO_2NH_2$; $-\overset{OH}{\underset{R^{27}}{\underset{|}{C}}}-\overset{O}{\underset{OH}{\underset{||}{P}}}-OH$;

      $-CONHNHSO_2CF_3$;

;   or $-\overset{O}{\underset{||}{C}}-NHSO_2-(CH_2)_s$;

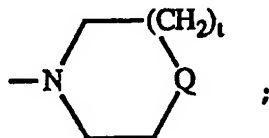R^{14} is H, alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{15} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3
to 6 carbon atoms, phenyl, benzyl, acyl of 1 to 4
carbon atoms, phenacyl;

R^{16} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3
to 6 carbon atoms, $(CH_2)_pC_6H_5$, OR^{17}, or $NR^{18}R^{19}$;

R^{17} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3
to 6 carbon atoms, phenyl or benzyl;

R^{18} and R^{19} independently are H, alkyl of 1 to 4 carbon
atoms, phenyl, benzyl, α-methylbenzyl, or taken

together with the nitrogen form a ring of the
formula;

$$-N\!\!\left\langle\begin{array}{c}-(CH_2)_t\\ \\ \end{array}\right\rangle Q \quad ;$$

Q is NR^{20}, O or CH_2;

R^{20} is H, alkyl of 1-4 carbon atoms, or phenyl;

R^{21} is alkyl of 1 to 6 carbon atoms, $-NR^{22}R^{23}$,
or $-CHCH_2CO_2CH_3$;
$|$
NH_2

R^{22} and R^{23} independently are H, alkyl of 1 to 6 carbon
atoms, benzyl, or are taken together as $(CH_2)_u$
where u is 3-6;

R^{24} is H, CH_3 or $-C_6H_5$;

R^{25} is $NR^{27}R^{28}$, OR^{28}, $NHCONH_2$, $NHCSNH_2$,

$$-NHSO_2\!\!-\!\!\left\langle\bigcirc\right\rangle\!\!-CH_3, \text{ or } -NHSO_2\!\!-\!\!\left\langle\bigcirc\right\rangle \quad ;$$

R^{26} is hydrogen, alkyl with from 1 to 6 carbon atoms,
benzyl, or allyl;

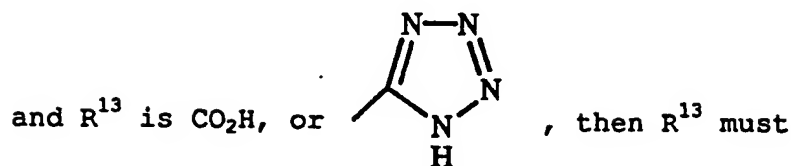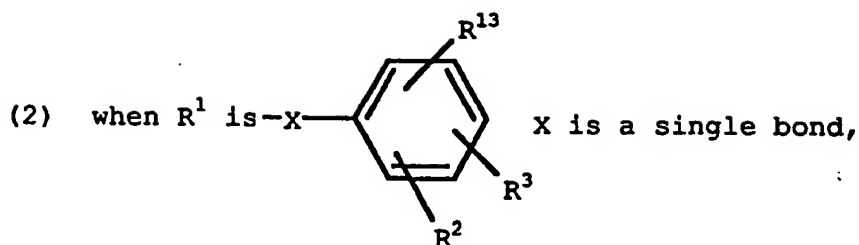R^{27} and R^{28} are independently hydrogen, alkyl with from 1 to 5 carbon atoms, or phenyl;

R^{29} and R^{30} are independently alkyl of 1-4 carbon atoms or taken together are $-(CH_2)_q-$;

R^{31} is H, alkyl of 1 to 4 carbon atoms, $-CH_2CH=CH_2$ or $-CH_2C_6H_4R^{32}$;

R^{32} is H, NO_2, NH_2, OH or OCH_3;

X is a carbon-carbon single bond, $-CO-$, $-CH_2-$, $-O-$, $-S-$,

$$-NH-, \quad -\underset{\underset{R^{26}}{|}}{N}-, \quad -\underset{\underset{R^{23}}{|}}{CON}-, \quad -\underset{\underset{R^{23}}{|}}{NCO}-, \quad -OCH_2-, \quad -CH_2O-,$$

$-SCH_2-$, $-CH_2S-$, $-NHC(R^{27})(R^{28})$, $-NR^{23}SO_2-$,

$-SO_2NR^{23}-$, $-C(R^{27})(R^{28})NH-$, $-CH=CH-$, $-CF=CF-$,

$-CH=CF-$, $-CF=CH-$, $-CH_2CH_2-$, $-CF_2CF_2-$,

$$\underset{\underset{-CH-}{}}{\overset{OR^{14}}{|}}, \quad \underset{\underset{-CH-}{}}{\overset{OCOR^{17}}{|}}, \quad \underset{\underset{-C-}{}}{\overset{NR^{25}}{\|}} \quad or \quad \underset{-C-}{\overset{R^{29}O \quad OR^{30}}{\diagdown\diagup}} \quad ;$$

Y is O or S;

Z is O, NR^{11}, or S;

m is 1 to 5;

n is 1 to 10;

p is 0 to 3;

q is 2 to 3;

r is 0 to 2;

s is 0 to 5;

t is 0 or 1;

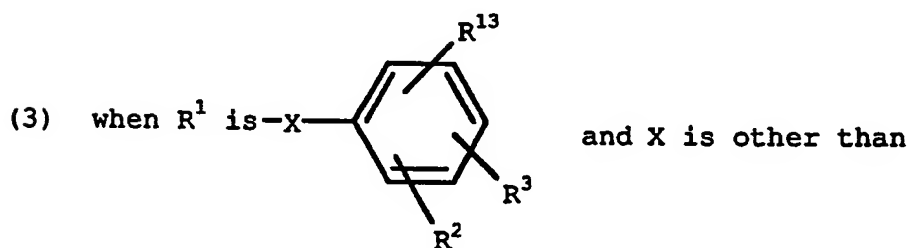and pharmaceutically acceptable salts of these compounds; provided that:

(1) the R^1 group is not in the ortho position;

(2) when R^1 is —X— [structure: benzene ring with R^{13}, R^3, R^2 substituents] X is a single bond,

and R^{13} is CO_2H, or [tetrazole structure: N—N / N / N—H] , then R^{13} must

be in the ortho or meta position; or when R^1 and X are as above and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, R^{13} must be ortho;

(3) when R^1 is —X— [structure: benzene ring with R^{13}, R^3, R^2 substituents] and X is other than

a single bond, then R^{13} must be ortho except when X = $NR^{23}CO$ and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, then R^{13} must be ortho or meta;

(4) when R^1 is 4-CO_2H or a salt thereof, R^6 cannot be S-alkyl;

(5) when R^1 is 4-CO_2H or a salt thereof, the substituent on the 4-position of the imidazole cannot be CH_2OH, CH_2OCOCH_3, or CH_2CO_2H;
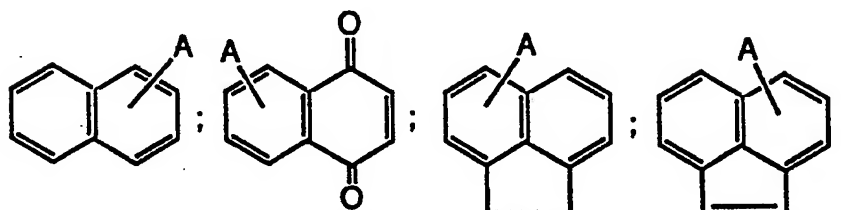
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(6)   when R^1 is -NHCO

$\text{CF}_3\text{SO}_2\text{HN}$

, R^6 is not methoxybenzyl;

(7)   the R^6 group is not -CHCH$_2$CH$_2$CH$_3$ or CH$_2$OH.

5

The R^7 substituents named above can be represented by the following formula:

1- or 2-naphthyl   5- or 6-naphtho-   3-, 4- or 5-   3-, 4- or 5-
                    quinonyl   acenaphthenyl   acenaphthyl
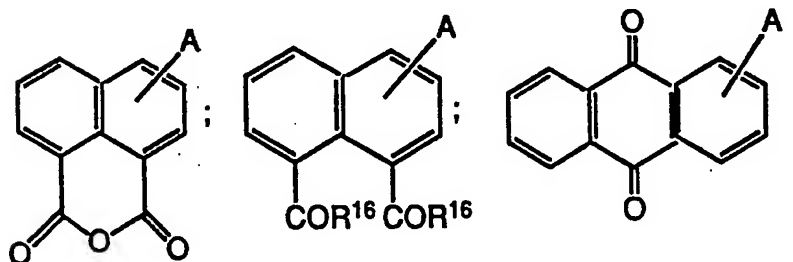
anhydride of 4,5-   4,5-disubstituted-   1- or 2-anthraquinonyl
dicarboxyl-1- or   1- or 2- naphthyl
2-naphthyl
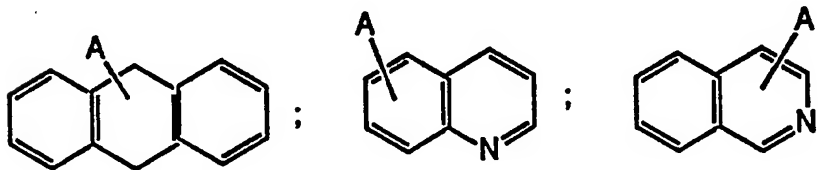
1-, 2- or 9-anthracenyl   2-, 3-, 4-, 5-,   1-, 3-, 4-, 5-,
                           6-, 7- or 8-   6-, 7- or 8-iso-
                           quinolinyl   quinolinyl

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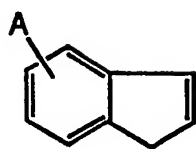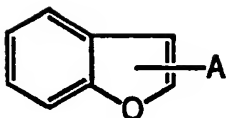
4-, 5-, 6- or 7-
indenyl

2-, 3-, 4-, 5-, 6- or
7-benzofuryl
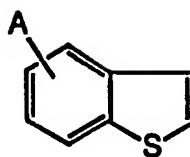
2-, 3-, 4-, 5-, 6- or
7-benzothienyl
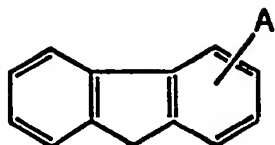
1-, 2-, 3- or 4-
fluorenyl

;

1-, 2-, 3- or 4-
dibenzofuryl

;

1-, 2-, 3- or 4-
dibenzothienyl

;
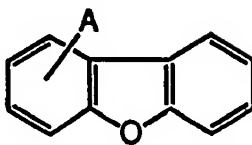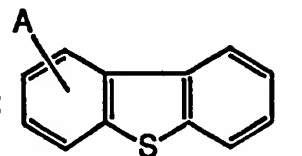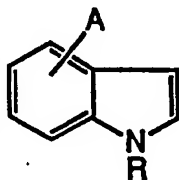
2-, 3-, 4-, 5-, 6-
or 7-indolyl

or
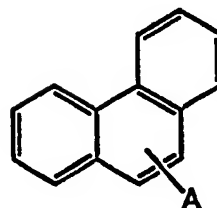
1-, 2-, 3-, 4- or 9-
phenanthrenyl

where A is a carbon-carbon single bond or a divalent
alkyl radical of 1-10 carbon atoms or a divalent alkenyl
or alkynyl radical fo 2-10 carbon atoms and R is
hydrogen, lower alkyl of 1-5 carbon atoms or benzyl.

Preferred for their antihypertensive activity are
novel compounds having the formula:

$$\text{(II)}$$

wherein

R^1 is $-CO_2H$; $-NHSO_2CF_3$;

or

R⁶ is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10
carbon atoms, alkynyl of 3 to 10 carbon atoms,
cycloalkyl of 3 to 8 carbon atoms, benzyl
substituted on the phenyl ring with up to two
groups selected from alkoxy of 1 to 4 carbon atoms,
halogen, alkyl of 1 to 4 carbon atoms, and nitro;

R^8 is $(CH_2)_m$-tetrazolyl, $-(CH_2)_n OR^{11}$; $-(CH_2)_n OCR^{14}$ (with $\overset{\displaystyle O}{\overset{\displaystyle \|}{}}$ on C);

$$-CH=CH(CH_2)_s \overset{O}{\overset{\|}{C}}R^{16}, \quad -CH=CH(CH_2)_s \overset{R^{14}}{\overset{|}{C}}HOR^{15};$$

$$-(CH_2)_n \overset{O}{\overset{\|}{C}}R^{16}; \quad -(CH_2)_n NHCOR^{10}; \quad -(CH_2)_n NHSO_2 R^{10};$$

$$-\overset{O}{\overset{\|}{C}}R^{16};$$

R^{13} is $-CO_2H$, $-CO_2R^9$, $NHSO_2CF_3$; SO_3H; or

R^{16} is H, alkyl of 1 to 5 carbon atoms, OR^{17}, or $NR^{18}R^{19}$;

X is carbon-carbon single bond, $-CO-$, $-CON-$,
                                              |
                                             R^{23}

$-CH_2CH_2-$, $-NCO-$, $-OCH_2-$, $-CH_2O-$, $-SCH_2-$,
              |
             R^{23}

$-CH_2S-$, $-NHCH_2-$, $-CH_2NH-$ or $-CH=CH-$; and

pharmaceutically acceptable salts of these
compounds.

More preferred are compounds of the preferred scope
where:

R^2 is H, alkyl of 1 to 4 carbon atoms, halogen, or
    alkoxy of 1 to 4 carbon atoms;

R^6 is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

R^7 is 1- or 2-naphthyl; 2-, 3-, or 4-quinolinyl;

5   1-, 3- or 4-isoquinolinyl, 1-, 2-, or 3-indolyl;

R^8 is $-(CH_2)_mOR^{11}$; $-(CH_2)_mOCR^{14}$; $-CH=CH-CHOR^{15}$;

10

$-(CH_2)_mCR^{16}$; $-CH_2NHCOR^{10}$;

15      $-(CH_2)_mNHSO_2R^{10}$; or $-COR^{16}$;

R^{10} is CF_3, alkyl of 1 to 6 carbon atoms or phenyl;

R^{11} is H, or alkyl of 1 to 4 carbon atoms;

R^{13} is CO_2H; $CO_2CH_2OCOC(CH_3)_3$; $NHSO_2CF_3$

20

        or   ;

R^{14} is H, or alkyl of 1 to 4 carbon atoms;

R^{15} is H, alkyl of 1 to 4 carbon atoms, or acyl of 1 to

25   4 carbon atoms;

R^{16} is H, alkyl of 1 to 5 carbon atoms; OR^{17}; or

             ;

30   m is 1 to 5;

     X = single bond, $-O-$; $-CO-$; $-NHCO-$; or $-OCH_2-$; and

        pharmaceutically acceptable salts.

19

Note that throughout the text when an alkyl
substituent is mentioned, the normal alkyl structure is
meant (i.e., butyl is n-butyl) unless otherwise
specified.

5   Pharmaceutically suitable salts include both the
metallic (inorganic) salts and organic salts; a list of
which is given in Remington's Pharmaceutical Sciences,
17th Edition, pg. 1418 (1985). It is well known to one
skilled in the art that an appropriate salt form is

10   chosen based on physical and chemical stability,
flowability, hydroscopicity and solubility. Preferred
salts of this invention for the reasons cited above
include potassium, sodium, calcium and ammonium salts.
        Also within the scope of this invention are

15   pharmaceutical compositions comprising a suitable
pharmaceutical carrier and a compound of Formula (I),
and methods of using the compounds of Formula (I) to
treat hypertension and congestive heart failure. The
pharmaceutical compositions can optionally contain one

20   or more other therapeutic agents, such as a diuretic or
a non-steroidal anti-inflammatory drug. Also within the
scope of this invention is a method of preventing renal
failure resulting from administration of a nonsteroidal
anti-inflammatory drug (NSAID) which comprises

25   administering a compound of Formula (I) in stepwise or
physical combination with the NSAID. The compounds of
this invention can also be used as diagnostic agents to
test the renin angiotensin system.
        It should be noted in the foregoing structural

30   formula, when a radical can be a substituent in more
than one previously defined radical, that first radical
can be selected independently in each previously defined
radical. For example, R^1, R^2 and R^3 can each be
$CONHOR^{12}$. R^{12} need not be the same substituent in each

of R^1, R^2 and R^3 but can be selected independently for
each of them.

Detailed Description

Synthesis

5   The novel compounds of Formula (I) may be prepared
using the reactions and techniques described in this
section. The reactions are performed in a solvent
appropriate to the reagents and materials employed and
suitable for the transformation being effected. It is

10 understood by those skilled in the art of organic
synthesis that the functionality present on the
imidazole and other portions of the molecule must be
consistent with the chemical transformations proposed.
This will frequently necessitate judgment as to the

15 order of synthetic steps, protecting groups required,
deprotection conditions, and activation of a benzylic
position to enable attachment to nitrogen on the
imidazole nucleus. Throughout the following section,
not all compounds of Formula (I) falling into a given

20 class may necessarily be prepared by all methods
described for that class. Substituents on the starting
materials may be incompatible with some of the reaction
conditions required in some of the methods described.
Such restrictions to the substituents which are

25 compatible with the reaction conditions will be readily
apparent to one skilled in the art and alternative
methods described must then be used.

21

Scheme 1
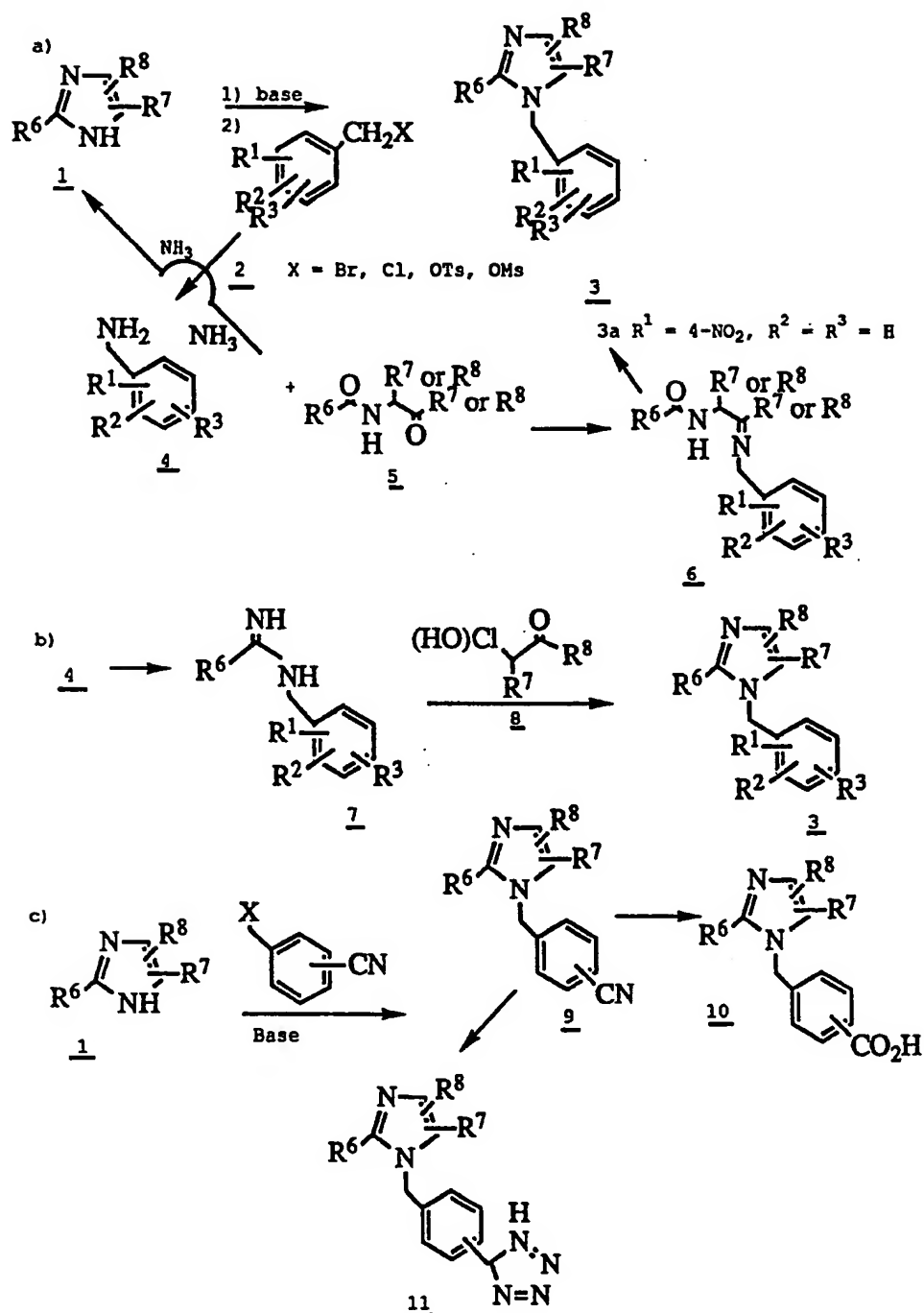
Generally, compounds of Formula (3) can be prepared
by direct alkylation onto imidazole (1), with an
appropriately protected benzyl halide, tosylate or

mesylate (2) in the presence of base, as shown in path
a). Preferably, the metallic imidazolid salt is
prepared by reacting imidazole (1) with a proton
acceptor such as MH where M is lithium, sodium or
5   potassium in a solvent such as dimethylformamide (DMF)
or by reacting it with a metal alkoxide of formula MOR
where R is methyl, ethyl, t-butyl or the like in an
alcohol solvent such as ethanol or t-butanol, or a
dipolar aprotic solvent such as dimethylformamide. The
10 imidazole salt is dissolved in an inert aprotic solvent
such as DMF, and treated with an appropriate alkylating
agent (2). Alternatively, imidazole (1) can be
alkylated with a benzyl halide (2, where X=Br, Cl) in
the presence of a base such as sodium carbonate,
15 potassium carbonate, triethylamine or pyridine. The
reaction is run in an inert solvent such as DMF or DMSO
at 20°C to the reflux temperature of the solvent for 1-
10 hours.

     For example, the 4-nitrobenzyl intermediate (3a,
20 wherein R^1 = 4-NO_2, R^2 = R^3 = H) may be obtained by
direct alkylation onto imidazole (1) with a 4-nitro-
benzyl halide, tosylate or mesylate in the presence of
base.

     As R^7 and R^8 are different, mixtures of two
25 regioisomer alkylation products (3b, and 3c) are
obtained in which R^7 and R^8 are interchanged. When R^8
is CHO the alkylation is such that the benzyl group
becomes attached to the adjacent nitrogen
preferentially. These isomers possess distinct physical
30 and biological properties and can usually be separated
and isolated by conventional separation techniques such
as chromatography and/or crystallization.

     In all series examined, the more rapidly eluted
isomer of a given pair has greater biological potency
35 than the less rapidly eluted isomer.

23

Alternatively, any properly functionalized
benzylamine derivative (4) may be converted to imine (6)
by treatment with an acylamino ketone (5) in the
presence of an inert solvent such as benzene, toluene,

5   or the like, and a catalytic amount of p-toluene-
sulfonic acid or molecular sieves, N. Engel, and W.
Steglich, Liebigs Ann. Chem., 1916, (1978), or in the
presence of alumina, F. Texier-Boulet, Synthesis, 679
(1985). The resulting imine (6) can be cyclized to the

10   N-benzyl imidazole (3) with phosphorus pentachloride
(PCl$_5$), phosphorus oxychloride (POCl$_3$) or
triphenylphosphine (PPh$_3$) in dichloroethane in the
presence of a base such as triethylamine, N. Engel and
W. Steglich, Liebigs Ann. Chem., 1916, (1978).

15   Acylamino ketone (5) is readily obtainable from
amino acids via the Dakin-West reaction, H.D. Dakin, R.
West, J. Biol. Chem., 78, 95 and 745 (1928), and various
modifications thereof, W. Steglich, G. Hofle, Angew.
Chem. Int. Ed. Engl., 8, 981 (1969); G. Hofle, W.

20   Steglich, H. Vorbruggen, Angew. Chem. Int. Ed. Engl.,
17, 569 (1978); W. Steglich, G. Hofle, Ber., 102, 883
(1969), or by selective reduction of acyl cyanides, A.
Pfaltz, S. Anwar, Tet. Lett. 2977 (1984), or from
α-halo, α-tosyl or α-mesyl ketones via the appropriate

25   substitution reactions that one skilled in the art will
readily recognize.

The functionalized benzylamines (4) may be made
from the corresponding benzyl halide, tosylate or
mesylate (2) via displacement with a nitrogen

30   nucleophile, a procedure familiar to one skilled in the
art. This displacement may be achieved using azide ion,
ammonia, or phthalimide anion, etc., in a neutral
solvent such as dimethylformamide, dimethylsulfoxide
etc., or under phase transfer conditions. The benzyl

35   halide (2) may be made by a variety of benzylic halo-

24

genation methods familiar to one skilled in the art, for example benzylic bromination of toluene derivatives with N-bromosuccinimide in an inert solvent such as carbon tetrachloride in the presence of a radical

5   initiator such as benzoyl peroxide at temperatures up to reflux conditions.

A wide variety of toluene derivatives may be made from simple electrophilic substitution reactions on an aromatic ring. This includes nitration, sulfonation,

10   phosphorylation, Friedel-Crafts alkylation, Friedel-Crafts acylation, halogenation, and other similar reactions known to one skilled in the art, G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. 1-5, Interscience, New York, (1965).

15   Another way to synthesize functionalized benzyl halides is via chloromethylation of the corresponding aromatic precursor. Thus, the appropriately substituted benzene ring may be chloromethylated with formaldehyde and hydrochloric acid (HCl) for example with or without

20   an inert solvent such as chloroform, carbon tetrachloride, light petroleum ether or acetic acid. A Lewis acid such as zinc chloride ($ZnCl_2$) or a mineral acid such as phosphoric acid may also be added as a catalyst or condensing agent, R. C. Fuson, C. H.

25   McKeever, Org. Reactions, 1, 63 (1942).

Alternatively, N-benzylimidazoles (3) can also be prepared as shown in path b) by forming an R^6 substituted amidine (7) from an appropriately substituted benzylamine (4) which is in turn reacted

30   with an α-haloketone, α-hydroxyketone (8), α-halo-aldehyde, or α-hydroxyaldehyde, F. Kunckell, Ber., 34, 637 (1901).

As shown in path a), imidazole (1) may be alkylated by a variety of benzyl derivatives. These include

35   compounds with latent acid functionalities such as o, m,

25

and p-cyanobenzylhalides, mesylates or tosylates as
shown in path c). Nitriles of formula (9) may be
hydrolyzed to carboxylic acids of formula (10) by
treatment with strong acid or alkali. Preferably,

5   treatment with a 1:1 (v/v) mixture of concentrated
aqueous hydrochloric acid/glacial acetic acid at reflux
temperatures for 2-96 hours or by treatment with 1N
sodium hydroxide in an alcohol solvent such as ethanol
or ethylene glycol for 2-96 hours at temperatures from

10 20°C to reflux can be used. If another nitrile group is
present it will also be hydrolyzed. The nitrile
functionality can also be hydrolyzed in two steps by
first stirring in sulfuric acid to form the amide
followed by hydrolysis with sodium hydroxide or a

15 mineral acid to give the carboxylic acid (10).

The nitriles (9) can be converted into the
corresponding tetrazole derivative (11) by a variety of
methods using hydrazoic acid. For example, the nitrile
can be heated with sodium azide and ammonium chloride in

20 DMF at temperatures between 30°C and reflux for 1-10
days, J. P. Hurwitz and A. J. Tomson, J. Org. Chem., 26,
3392 (1961). Preferably, the tetrazole is prepared by
the 1,3-dipolar cycloaddition of trialkyltin or
triaryltin azides to the appropriately substituted

25 nitrile as described in detail by Scheme 15.

The starting imidazole compounds (1) are readily
available by any of a number of standard methods. For
example, acylaminoketone (5) can be cyclized with
ammonia or equivalents thereof, D. Davidson, et al., J.

30 Org. Chem., 2, 319 (1937) to the corresponding imidazole
as shown in Scheme 1. The corresponding oxazole can
also be converted to imidazole (1) by action of ammonia
or amines in general, H. Bredereck, et al., Ber., 88,
1351 (1955); J. W. Cornforth and R. H. Cornforth, J.

35 Chem Soc., 96, (1947).

26

Several alternative routes to imidazoles (1) are
illustrated in Scheme 2. As shown in Scheme 2 equation
a), reaction of the appropriate R^6 substituted imidate
esters (12) with an appropriately substituted α-hydroxy-
5   or α-haloketone or aldehyde (8) in ammonia leads to
imidazoles of formula (1), P. Dziuron, and W. Schunack,
Archiv. Pharmaz., 307 and 470 (1974).

The starting imidazole compounds (1) wherein R^7 and
R^8 are both hydrogen can be prepared as shown in
10   equation b) by reaction of the appropriate
R^6-substituted imidate ester (12) with α-amino-
acetaldehyde dimethyl acetal (13), M. R. Grimmett, Adv.
Heterocyclic Chem., 12, 103 (1970).

As shown in equation c), imidazole (15; wherein
15   R^7 = hydrogen and R^8 = CH_2OH) can be prepared by
treatment of the imidate ester (12) with 1,3-dihydroxy-
acetone (14) in ammonia by the procedure described in
Archive der Pharmazie, 307, 470 (1974). Halogenation of
imidazole (15) or any imidazole wherein R^7 or R^8 is
20   hydrogen is preferably accomplished by reaction with one
to two equivalents of N-halosuccinimide in a polar
solvent such as dioxane or 2-methoxyethanol at a
temperature of 40-100°C for 1-10 hours. Reaction of the
halogenated imidazole (16) with a benzylhalide (2) in
25   the manner described in Scheme 1 affords the
corresponding N-benzylimidazole (17); wherein R^7 is
halogen and R^8 is CH_2OH). This procedure is described
in U.S. Patent 4,355,040. Alternatively, imidazole (17)
can be prepared by the procedure described in U.S.
30   Patent 4,207,324.

Compounds of formula (17) can also be prepared by
treatment of the starting imidazole compound (1) wherein
R^7 and R^8 are both hydrogen, with the appropriate benzyl
halide followed by functionalization of R^7 and R^8 by
35   treatment with formaldehyde as described in E. F.

27

Godefroi, et al., <u>Recueil</u>, 91, 1383 (1972) followed by
halogenation as was described above.

As shown in equation d) the imidazoles ($\underline{1}$) can also
be prepared by reaction of R^6 substituted amidines ($\underline{18}$)
5   with an α-hydroxy- or α-haloketone or aldehyde ($\underline{8}$) as
described by F. Kunckel, <u>Ber.</u>, <u>34</u>, 637, (1901).

Compounds of Formula ($\underline{1}$) wherein $R^8 = CH_2OH$ can be
prepared as shown in equation e). The imidazoles ($\underline{1}$)
were prepared as described in L. A. Reiter, <u>J. Org.</u>
10   <u>Chem.</u>, <u>52</u>, 2714 (1987). Hydroxymethylation of ($\underline{1}$) as
described by U. Kempe, et al. in U.S. Patent 4,278,801
provides the hydroxymethylimidazoles ($\underline{1a}$).

Scheme 2

a)

$$\underset{12}{\overset{NH\cdot HCl}{\underset{R^6}{\underset{OCH_2CH_3}{|}}}} + \underset{8}{(Cl)HO\underset{R^7}{\overset{O}{\underset{|}{\parallel}}}R^8} \quad \xrightarrow{NH_3} \quad \underline{1}$$

b) $\underline{12}$ + H$_2$NCH$_2$CH(OMe)$_2$ $\longrightarrow$ R^6—imidazole

$\underline{13}$

$\underline{1}$ (wherein R^7 = R^8 = H)

c) $\underline{12}$ +

$$\begin{array}{c} CH_2OH \\ | \\ C=O \\ | \\ CH_2OH \end{array}$$

$\xrightarrow{NH_3}$

R^6—imidazole—OH

$\underline{14}$

$\underline{15}$

halogenation

$\underline{16}$

$\xrightarrow[X = Br, I]{(2)}$

$\underline{17}$

d)

$$\underset{18}{\overset{NH}{\underset{R^6}{\underset{NH_2}{|}}}} + \underset{8}{(Cl)HO\underset{R^7}{\overset{O}{\underset{|}{\parallel}}}R^8} \quad \xrightarrow{NH_3} \quad \underline{1}$$

e)   RCOCH$_2$OH+R^{6}CHO $\xrightarrow[\text{2) H}_2\text{S}]{\text{1) NH}_3, \text{ Cu}^{+2}}$ imidazole

R = naphthyl, quinolinyl, etc.

$\underline{1}$

H$_3$O$^+$, CH$_2$O

$\underline{1a}$

29

Scheme 3

a)

17 $\longrightarrow$ 25 $\longrightarrow$ 26

$\underline{\text{HCl/HOAc}}$
or NaOH

27 $\xrightarrow{\text{HCl/MeOH}}$ 28

b) 17 $\xrightarrow[\substack{\text{or} \\ R^{14}COCl}]{(R^{14}C)_2O}$ 29

c) 17 $\longrightarrow$ 30 $\longleftarrow$ 25
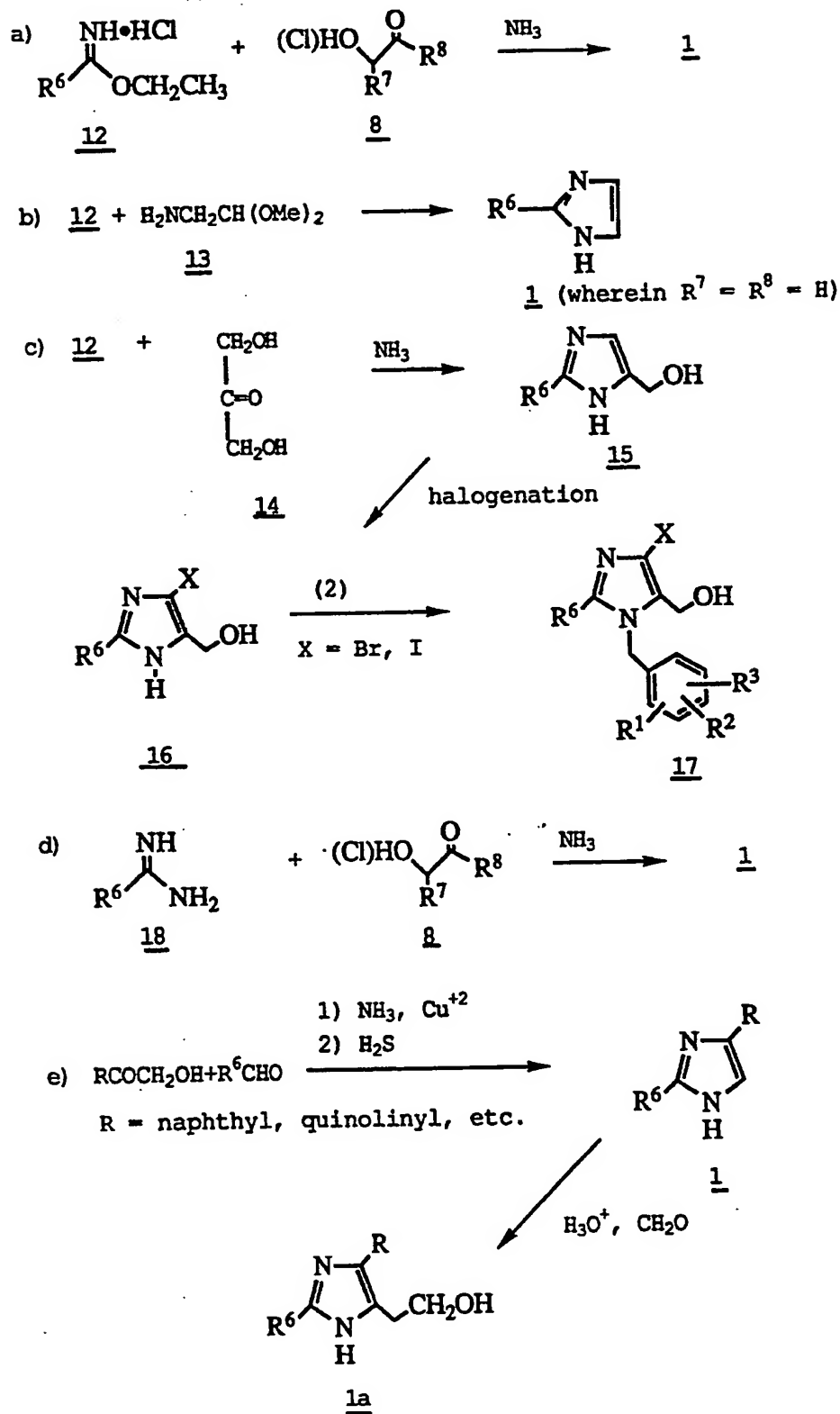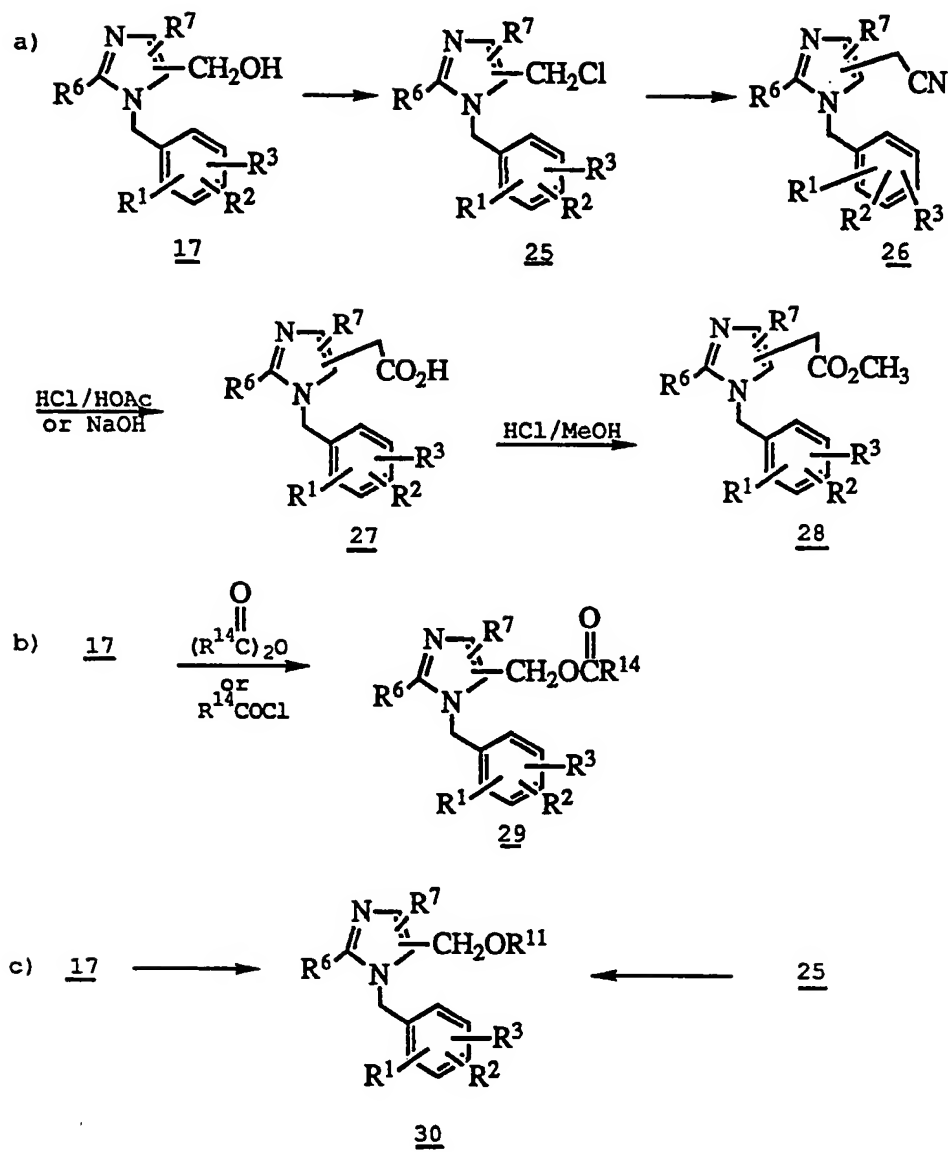
As shown in Scheme 3, path a) for benzylimidazoles
(17) where R^8 = CH_2OH, the hydroxymethyl groups may be
easily converted to the corresponding halide, mesylate
or tosylate by a variety of methods familiar to one
5   skilled in the art. Preferably, the alcohol (17) is
converted to the chloride (25) with thionyl chloride in
an inert solvent at temperatures of 20°C to the reflux
temperature of the solvent.

Chloride (25) may be displaced by a variety of
10 nucleophiles by nucleophilic displacement reaction
procedures familiar to one skilled in the art. For
example, excess sodium cyanide in DMSO may be used to
form cyanomethyl derivatives (26) at temperatures of
20°C to 100°C.

15   Nitrile (26) may be hydrolyzed to an acetic acid
derivative (27), by a variety of methods. These methods
include methods described previously for the hydrolysis
of nitriles of formula (9). Examples of desired acids
and bases for this hydrolysis include mineral acids such
20 as sulfuric acid, hydrochloric acid, and mixtures of
either of the above with 30-50% acetic acid (when
solubility is a problem), and alkali metal hydroxides
such as sodium hydroxide or potassium hydroxide. The
hydrolysis reaction proceeds under heating at
25 temperatures ranging from 50-160°C for 2-48 hours.
Carboxylic acid (27) may be esterified by a variety of
methods without affecting other parts of the molecule.
Preferably, (27) is refluxed in a hydrochloric
acid/methanol solution for 2-48 hours to give ester
30 (28).

Ester (28) may be hydrolyzed to carboxylic acid
(27), for instance, after R^1, R^2 and R^3 have been
elaborated. Various methods, acidic or basic, may be
used. For example, compound (28) is stirred with 0.5N
35 potassium hydroxide in methanol, or if base soluble, it

is stirred in 1.0N sodium hydroxide for 1-48 h at 20°C
to reflux temperatures.

Hydroxymethyl derivative (17) may be acylated to
give (29) by a variety of procedures. As shown in path

5   b) acylation can be achieved with 1-3 equivalents of an
acyl halide or an anhydride in a solvent such as diethyl
ether, tetrahydrofuran, methylene chloride or the like
in the presence of a base such as pyridine or
triethylamine. Alternatively (17) may be acylated by

10 reaction with a carboxylic acid and dicyclohexylcarbo-
diimide (DCC) in the presence of a catalytic amount of
4-(N,N-dimethylamino)pyridine (DMAP) via the procedure
described by A. Hassner, Tet. Lett., 46, 4475 (1978).
Treatment of (17) with a solution of carboxylic acid

15 anhydride in pyridine optionally with a catalytic amount
of DMAP at temperatures of 20-100°C for 2-48 hours is
the preferred method.

The ether (30) can be prepared from the alcohol
(17) as shown in path c) by methods such as treatment of

20 (17) in a solvent such as dimethylformamide or
dimethylsulfoxide with potassium t-butoxide, sodium
hydride, or the like followed by treatment with $R^{11}L$ at
25°C for 1-20 hours, where L is a halogen, tosylate or
mesylate.

25 Alternatively, treatment of (17) with 1-5
equivalents of thionyl chloride in chloroform for 2-6
hours at 25°C followed by treatment of the intermediate
(25) with 1-3 equivalents of MOR^{11}, where M is sodium or
potassium, for 2-10 hours at 25°C either in $R^{11}OH$ as

30 solvent or in a polar solvent such as dimethylform-
amide or the like will also yield ether (30).

The ether (30) can also be prepared for example by
heating (17) for 3-15 hours at 60-160°C in $R^{11}OH$
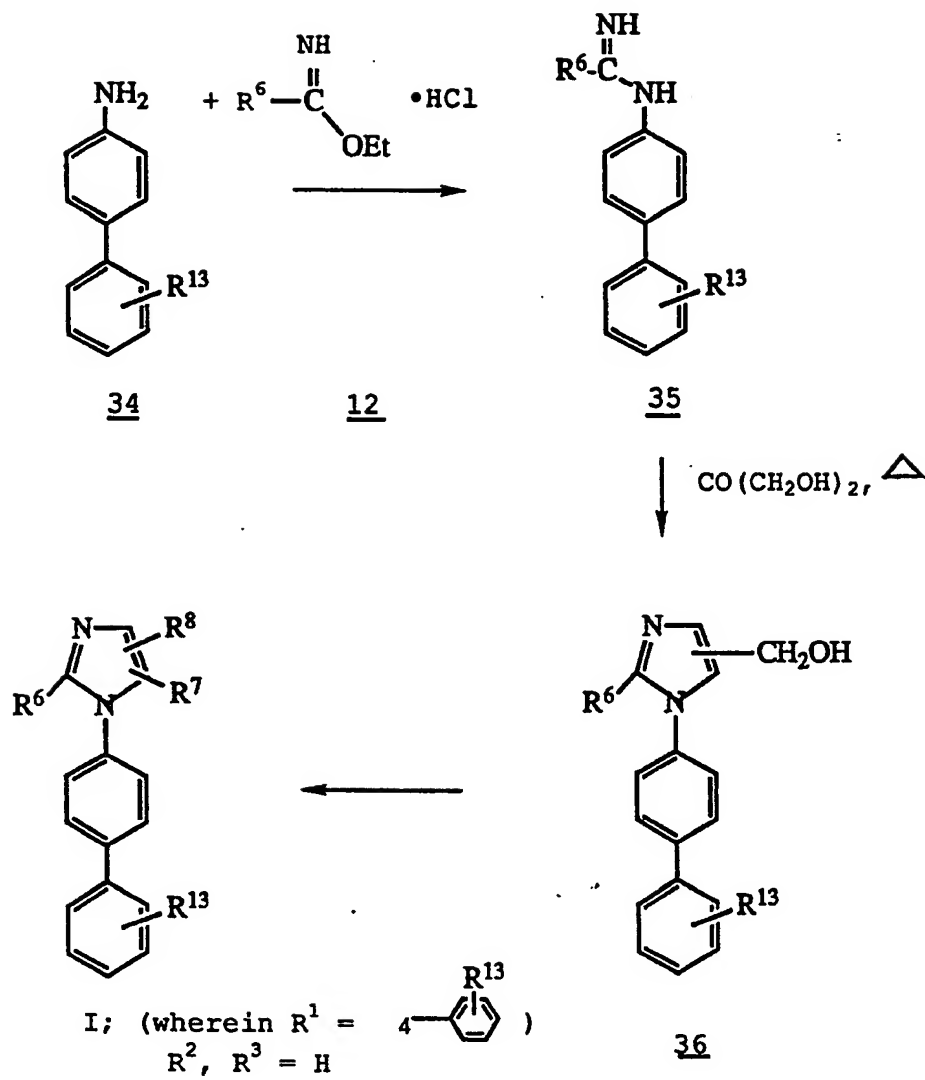containing an inorganic acid such as a hydrochloric acid

35 or sulfuric acid.

N-arylimidazoles of formula I (compounds wherein
r=o) can be prepared by the following methods, it being
understood by one skilled in the art that certain
manipulations, protecting and deprotecting steps, and
5   other synthetic procedures disclosed above may be
necessary to produce compounds with the desired
combinations of R^6, R^7, R^8 and R^{13}.

As shown in Scheme 4, equation a) the reaction of
aniline derivative (34) with imidate ester (12) to form
10   the substituted amidine (35) provides material which can
be cyclized with dihydroxyacetone to form structure
(36). Subsequent elaboration into (I) provides the
N-arylimidazole compounds of the invention.

Alternatively as shown by equation b) the Marckwald
15   procedure, described by Marckwald et al., Ber., 22, 568,
1353 (1889); Ber., 25, 2354 (1892) can form a
2-mercaptoimidazole (38) from aniline derivative (34)
via isothiocyanate (37). Desulfurization of (38) with
dilute nitric acid followed by anion formation at the
20   2-position of the imidazole (39) and reaction with R^6X
where X is Cl, Br, I, allows the formation of (40) which
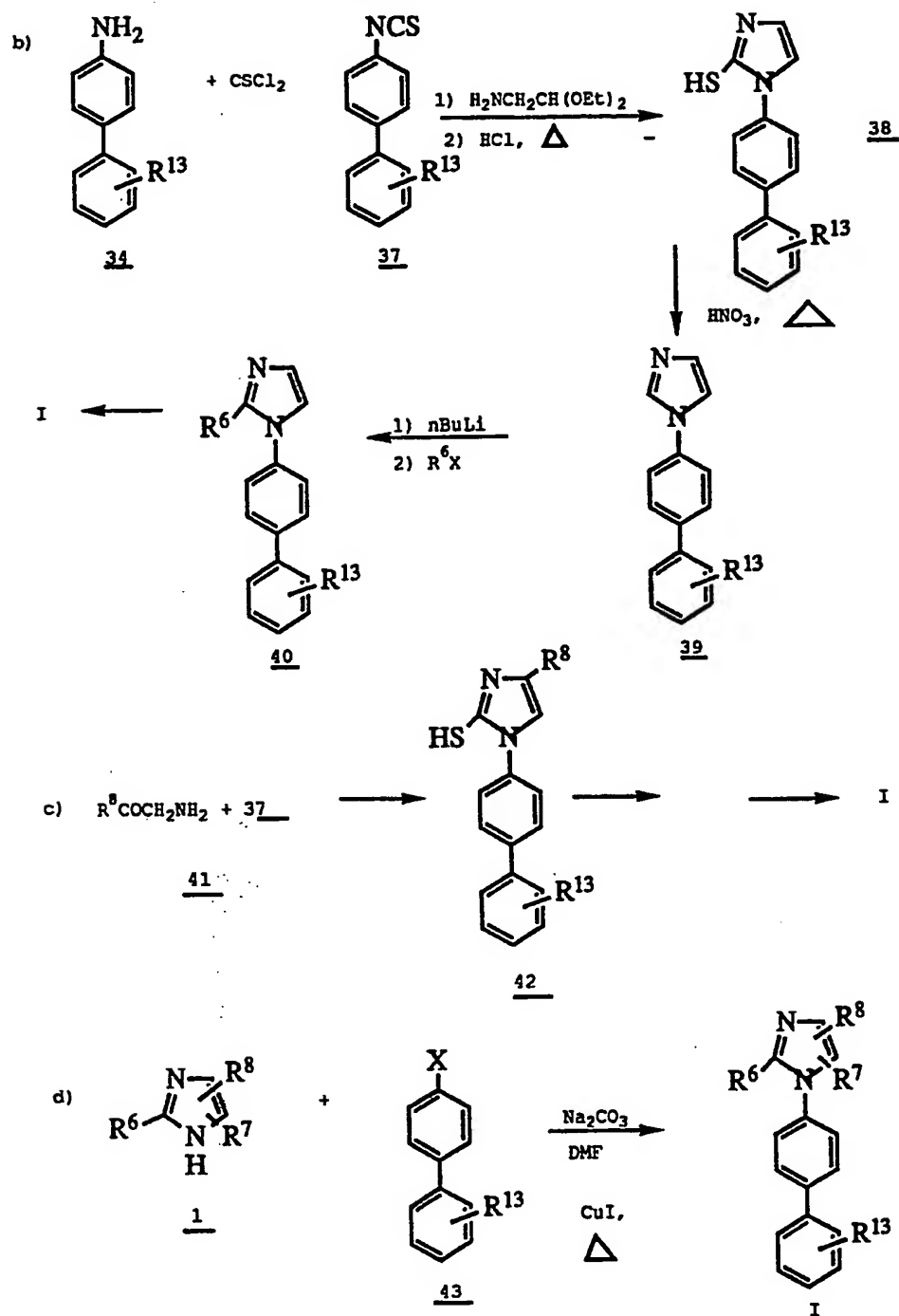can be subsequently elaborated to I.

A variation of Marckwald's process as shown in
equation c) using an α-aminoketone (41) and
25   isothiocyanate (37) can also be employed, see Norris and
McKee, J. Amer. Chem. Soc., 77, 1056 (1955) can also be
employed. Intermediate (42) can be converted to (I) by
known sequences. The general procedure of Carboni et
al., J. Amer. Chem. Soc., 89, 2626 (1967) (illustrated
30   by equation d)) can also be used to prepare N-aryl
substituted imidazoles from appropriate haloaromatic
compounds (43; X=F, Cl, Br) and imidazoles (1):

33

Scheme 4

I; (wherein R^1 = 4—$\langle$ R^{13} $\rangle$)
R^2, R^3 = H

34

Scheme 4 (continued)

b)

1) $H_2NCH_2CH(OEt)_2$
2) HCl, △

c) $R^8COCH_2NH_2$ + 37

<u>41</u>

d)

Na_2CO_3
DMF

CuI,
△

In various synthetic routes R^1, R^2 and R^3 do not necessarily remain the same from the starting compound to the final products, but are often manipulated through

35

known reactions in the intermediate steps as shown in
Schemes 5-22. All of the transformations shown in
Schemes 5-10 and 12 can also be carried out on the
terminal aromatic ring (i.e., biphenyl ring).

5

Scheme 5

44   45   46
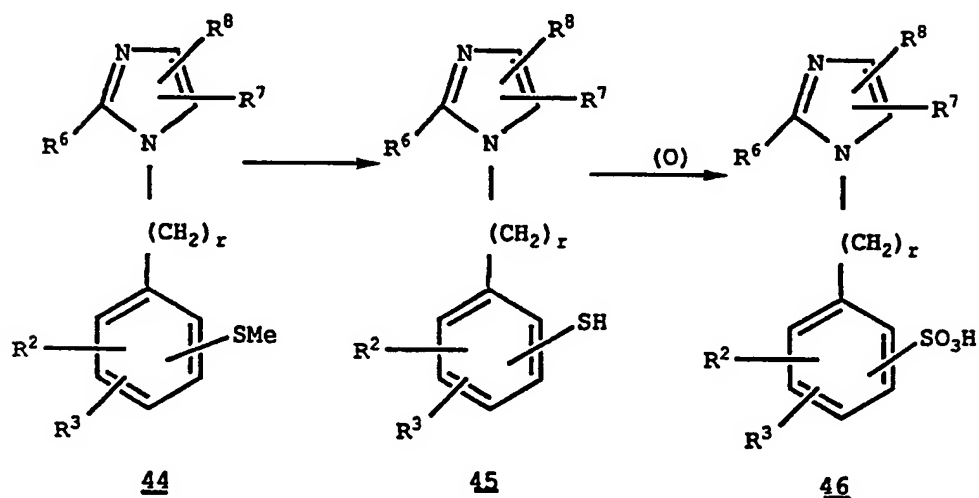
10   As shown in Scheme 5, compounds where R¹ is a
sulfonic acid group may be prepared by oxidation of the
corresponding thiol (45). Thus, an N-benzylimidazole
derivative bearing a thiol group may be converted into a
sulfonic acid (46) by the action of hydrogen peroxide,
15 peroxyacids such as metachloroperoxybenzoic acid,
potassium permanganate or by a variety of other
oxidizing agents, E. E. Reid, Organic Chemistry of
Bivalent Sulfur, 1, Chemical Publishing Co., New York,
120-121 (1958).

20   Aromatic hydroxy or thiol groups are obtained from
deprotection of the corresponding alkyl ether or
thioethers. Thus, for example, a methyl ether or a
methyl thioether derivative (44) of an N-benzylimid-
azole containing one or more aromatic rings may be
25 converted into the free phenol or thiophenol (45) by the

action of boron tribromide methyl sulfide, P. G. Willard
and C. F. Fryhl , Tet. Lett., 21, 3731 (1980);
trimethylsilyl iodide, M. E. Jung and M. A. Lyster, J.
Org. Chem., 42, 3761 (1977); KSEt and derivatives

5   thereof, G. I. Feutrill, R. N. Mirrington, Tet. Lett.,
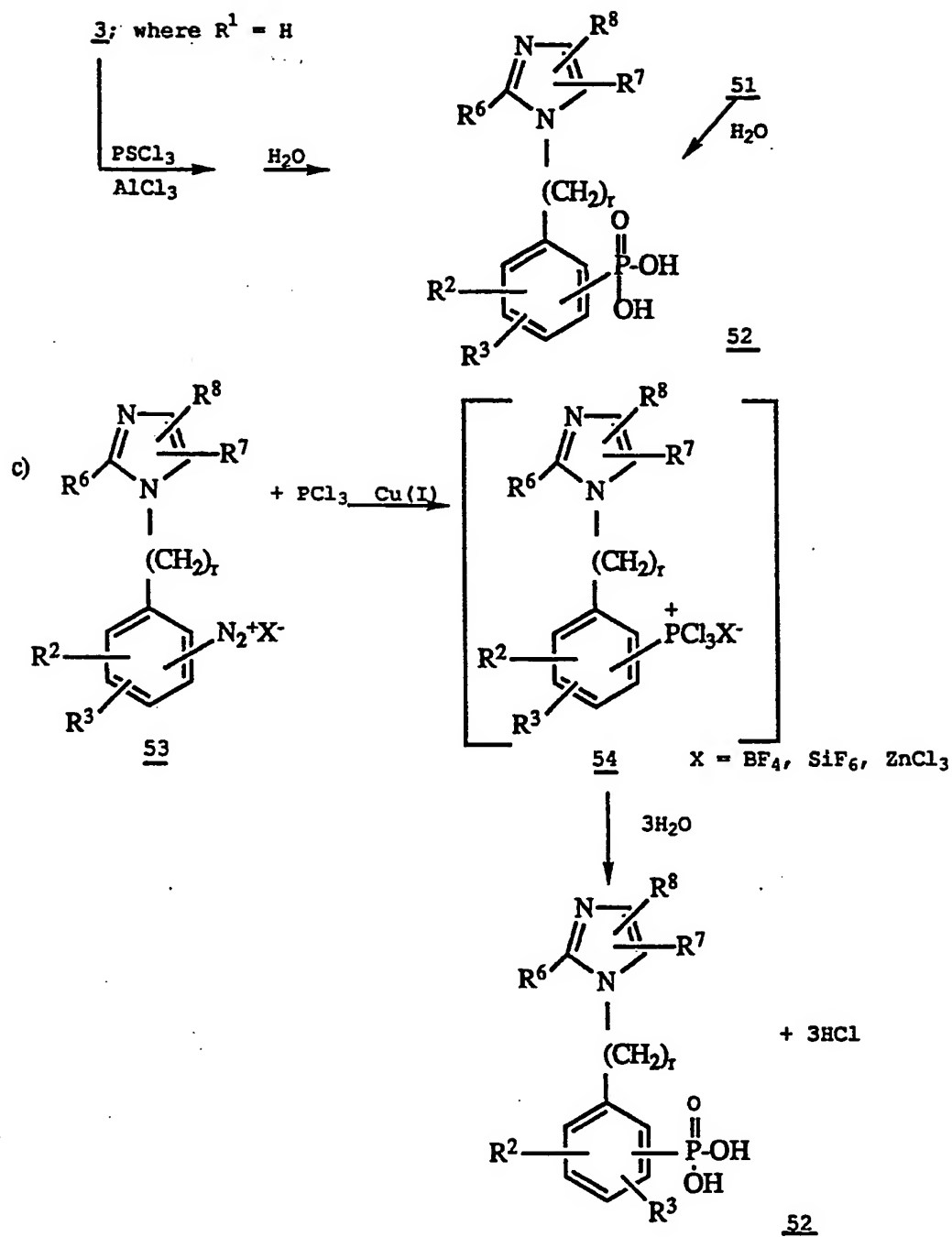1327, (1970), and a variety of other reagents.

    Alternatively, N-benzylimidazoles may be sulfonated
by stirring with H_2SO_4 at a variety of different
concentrations or with other sulfonating agents such as

10   chlorosulfonic acid or sulfur trioxide with or without
complexing agents such as dioxane or pyridine at
temperatures from 0 to 200°C with or without solvent, K.
LeRoi Nelson in Friedel-Crafts and Related Reactions,
III part 2, G. A. Olah, ed., Interscience Publ., 1355

15   (1964).

    The synthesis of compounds where R^1 is a sulfate,
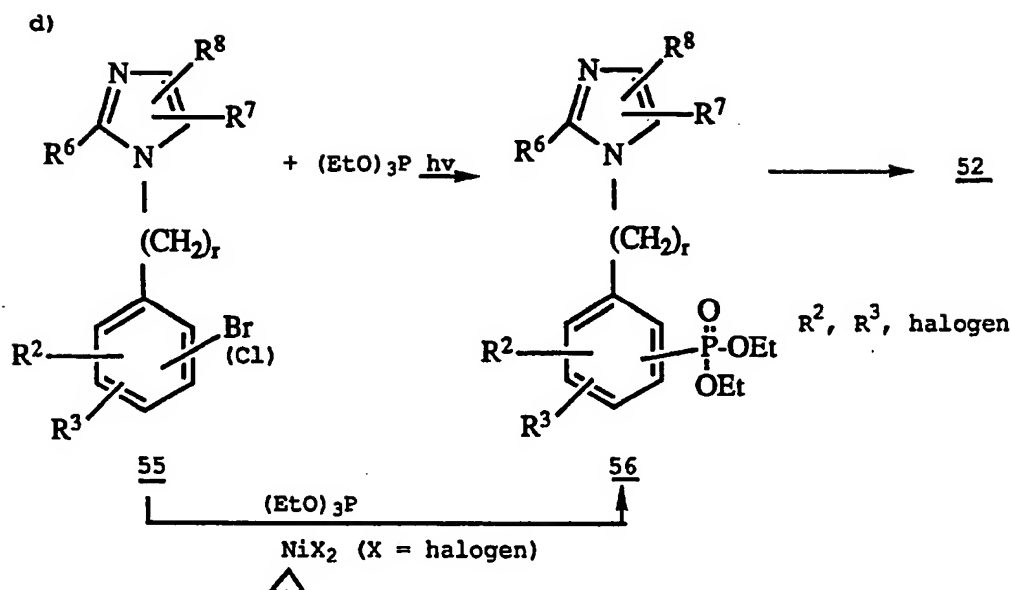phosphate or phosphonic acid are depicted in Scheme 6:

37

Scheme 6

a)

47

48

49

b)

3

50

51

38

Scheme 6 (continued)

<u>3</u>; where R^1 = H

$\xrightarrow[\text{AlCl}_3]{\text{PSCl}_3}$ $\xrightarrow{\text{H}_2\text{O}}$

$\xrightarrow[\text{H}_2\text{O}]{\underline{51}}$

52

c)

$+ \text{PCl}_3 \xrightarrow{\text{Cu(I)}}$

53

54   X = BF$_4$, SiF$_6$, ZnCl$_3$

$\downarrow$ 3H$_2$O

+ 3HCl

52
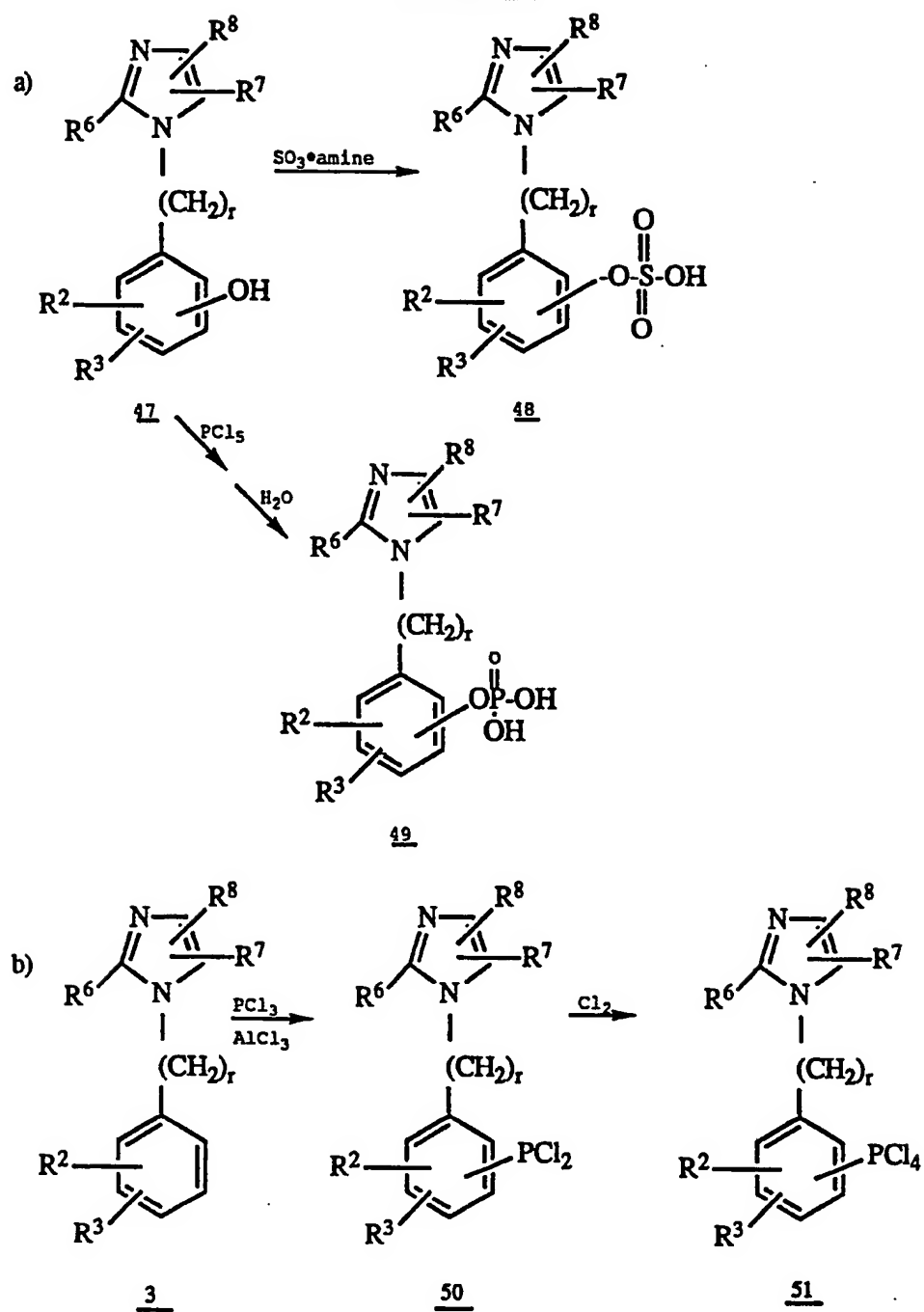
Scheme 6 (continued)

d)

N-Benzylimidazoles containing a phenolic hydroxyl
group (47) may be readily converted into the
5 corresponding sulfate (48) or phosphate (49). As shown
in equation a), reaction of the phenol with a sulfur
trioxide-amine complex will give the corresponding
sulfate (48), E. E. Gilbert, Sulfonation and Related
Reactions, Interscience, New York, chapter 6 (1965).
10 Reaction of the phenol (47) with phosphorus penta-
chloride followed by hydrolysis will give the
corresponding phosphate (49), G. M. Kosolapoff,
Organophosphorus Compounds, John Wiley, New York, 235
(1950).

15   As shown in equation b) N-benzylimidazoles may be
converted into the corresponding phosphonic acids by
reaction with phosphorus trichloride (PCl$_3$) and aluminum
chloride (AlCl$_3$) in an inert solvent for 0.5-96 hours
from temperatures of 25°C to the reflux temperatures of
20 the solvent. Appropriate workup followed by reaction
with chlorine (Cl$_2$) and subsequent hydrolysis of the

40

tetrachloride (51) gives the phosphonic acid derivative
(52), G. M. Kosolapoff in Org. Reactions, 6, R. Adams,
editor, John Wiley and Sons, New York, 297 (1951).
Another more direct route involves reaction of the N-
5   benzylimidazole with $PSCl_3$ and $AlCl_3$ followed by
hydrolysis, R. S. Edmunson in Comprehensive Organic
Chemistry, Vol. 2, D. Barton and W. D. Ollis editors,
Pergamon Press, New York, 1285 (1979).

Alternatively, equation c) illustrates that aryl
10   phosphonic acids (52) may be formed from reaction of the
corresponding diazonium salt (53) with PCl_3 in the
presence of Cu(I) followed by hydrolysis with water
(ibid, p. 1286).

As shown in equation d), the aryl halides (55) may
15   be photolyzed in the presence of phosphite esters to
give phosphonate esters (56), R. Kluger, J. L. W. Chan,
J. Am. Chem. Soc., 95, 2362, (1973). These same aryl
halides also react with phosphite esters in the presence
of nickel or palladium salts to give phosphonate esters,
20   P. Tavs, Chem. Ber., 103, 2428 (1970), which can be
subsequently converted to phosphonic acids (52) by
procedures known to one skilled in the art.

N-Benzylimidazoles containing an aldehyde or ketone
(57) may be reacted with a phosphorus trihalide followed
25   by water hydrolysis to give α-hydroxyphosphonic acid
derivatives, G.M. Kosolapoff, op. cit., 304, as shown in
Scheme 7.

41

Scheme 7

57   (R = H, or alkyl)   58
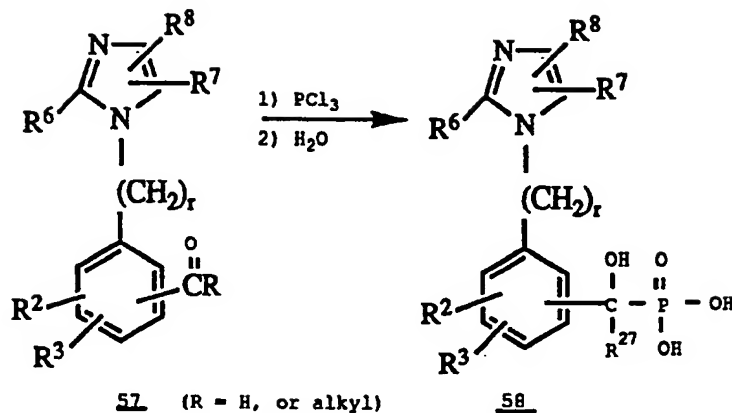
5   Compounds where R^1 is $-CONHOR^{12}$ may be prepared as
shown in Scheme 8, by the treatment of a carboxylic acid
(10) with 1-4 equivalents of thionyl chloride for 1-10
hours. This reaction can be run without solvent or in a
nonreactive solvent such as benzene or chloroform at
10   temperatures of 25-65°C. The intermediate acid chloride
is then treated with 2-10 equivalents of the appropriate
amine derivative, H_2N-OR^{12}, for 2-18 hours at
temperatures of 25-80°C in a polar aprotic solvent such
as tetrahydrofuran or dimethylsulfoxide to give the
15   hydroxamic acid (59).

42

<u>Scheme 8</u>
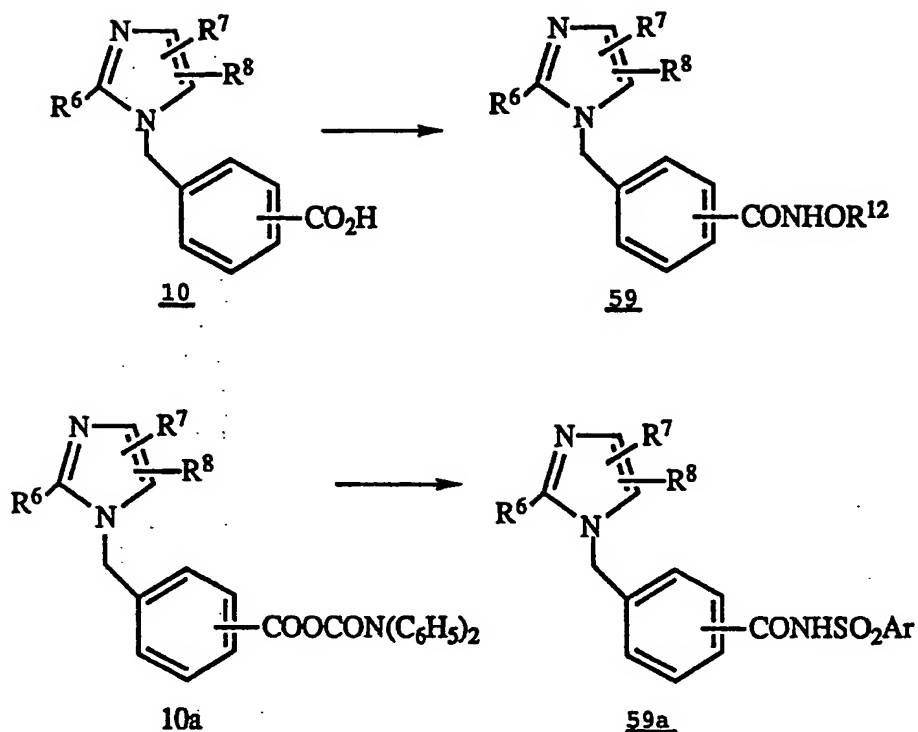
5   Alternatively, the carboxylic acid (10) can be
converted to the hydroxamic acid (59) according to the
procedure in <u>J. Med. Chem.</u>, <u>28</u>, 1158 (1985) by employing
dicyclohexylcarbodiimide, 1-hydroxybenzo-triazole, and
H_2NOR^{12} or according to the procedure described in

10   <u>Synthesis</u>, 929 (1985) employing the Vilsmeier reagent
and H_2NOR^{12}.

Compounds where R^1 is $-CONHSO_2Ar$ (59a, Ar=phenyl,
o-tolyl, etc.) may be produced by treatment of the
intermediate acid chlorides from the preparation of the

15   hydroxamic acids (59), with $ArSO_2NHNa$. Alternatively,
these acylsulfonamides (59a) can be prepared from the
carboxylic acids (10) through the corresponding N,N-
diphenylcarbamoyl anhydrides (10a) as described by F. J.
Brown, et al. in Eur. Pat. Appl. EP 199543 (<u>see Scheme</u>

20   <u>8</u>).

43

Scheme 9
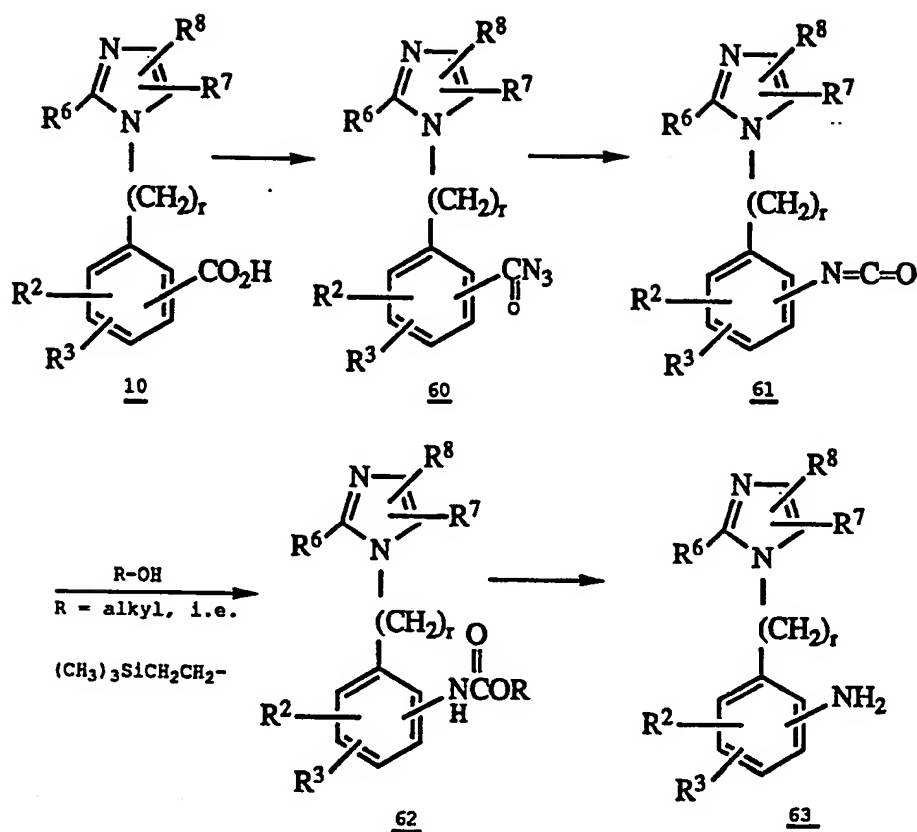
Aniline intermediates (63) are disclosed in U.S.
Patent No. 4,355,040 and may be obtained from the
corresponding nitro compound precursor by reduction. A
variety of reduction procedures may be used such as
iron/acetic acid, D. C. Owsley, J. J. Bloomfield,
Synthesis, 118, (1977), stannous chloride, F. D.
Bellamy, Tet. Lett., 839, (1984) or careful hydro-
genation over a metal catalyst such as palladium.

As shown in Scheme 9, aniline intermediates of
N-benzylimidazoles may also be prepared from the
corresponding carboxylic acid (10) or acid chloride via
a Curtius rearrangement of an intermediate acyl azide
(60). More modern methods include using diphenyl-

44

phosphoryl azide as a source of azide, T. Shioiri,
K. Ninomiya, S. Yamada, J. Am. Chem. Soc., 94, 6203
(1972), and trapping the intermediate isocyanate (61)
produced by the Curtius rearrangement with 2-trimethyl-

5   silylethanol and cleaving the resultant carbamate (62)
with fluoride to liberate the amine (63), T. L. Capson
and C. D. Poulter, Tet. Lett., 25, 3515 (1984).
Classical procedures familiar to one skilled in the art
may also be employed.

10   Compounds where R^1 is $-SO_2NH_2$ may be made
as shown in Scheme 10:

45

Scheme 10

$$\underset{64}{} \xrightarrow{\text{NH}_3} \underset{65}{}$$
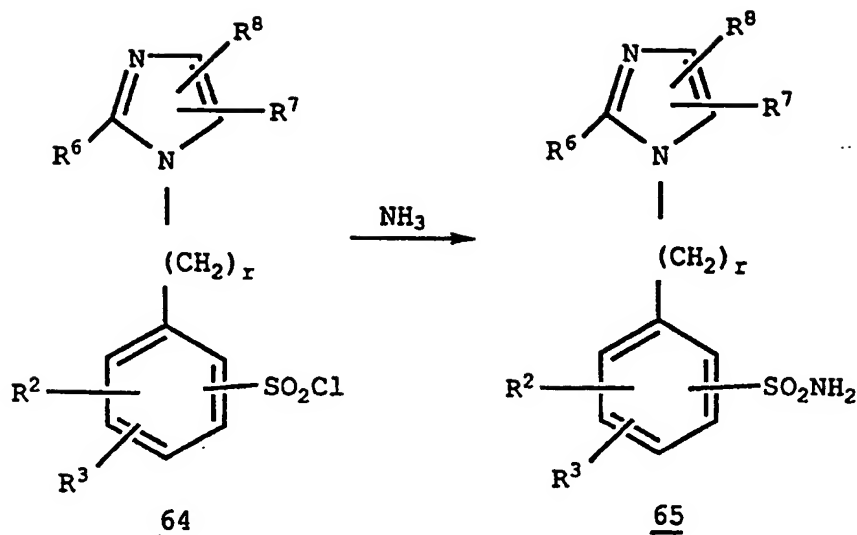
5   Sulfonamide compounds (65) may be made by reacting
an arylsulfonyl chloride (64) with ammonia, or its
equivalent. Unsubstituted arylsulfonamides are made by
reaction with ammonia in aqueous solution or in an inert
organic solvent, F. H. Bergheim and W. Braker, J. Am.
10 Chem. Soc., 66, 1459 (1944), or with dry powdered
ammonium carbonate, E. H. Huntress and J. S. Autenrieth,
J. Am. Chem. Soc., 63, 3446 (1941); E. H. Huntress and
F. H. Carten, J. Am. Chem. Soc., 62, 511 (1940).

     The sulfonyl chloride precursor may be prepared by
15 chlorosulfonation with chlorosulfonic acid on the
aromatic ring directly, E. H. Huntress and F. H. Carten,
ibid.; E. E. Gilbert, op. cit., 84, or by reacting the
corresponding aromatic diazonium chloride salt (53) with
sulfur dioxide in the presence of a copper catalyst, H.
20 Meerwein, et al., J. Prakt. Chem., [ii], 152, 251
(1939), or by reacting the aromatic sulfonic acid (46)
with PCl$_5$ or POCl$_3$, C. M. Suter, The Organic Chemistry
of Sulfur, John Wiley, 459 (1948).

46

Linked ester compounds of formula (I) where R^1

$$\overset{O}{\overset{\|}{}}$$

5   is $-CO_2CH(R^{24})OCR^{21}$ can be made by procedures well known

in penicillin and cephalosporin chemistry. The purpose

is to provide materials which are more lipophilic and

which will be useful orally by rapid transit from the

gut into the bloodstream, and which will then cleave at

10   a sufficiently rapid rate to provide therapeutically

useful concentrations of the active carboxylic acid

form. The following review articles and references

cited therein discuss this concept and the chemistry

involved in preparing such compounds V. J. Stella, et

15   al., Drugs, 29, 455-473 (1985); H. Ferres, Drugs of

Today. 19 (9), 499-538 (1983); A. A. Sirkula, Ann.

Repts. Med. Chem., 10, 306-315 (1975).

Experimental procedures which are applicable to the

preparation of chemically stable linked esters are

20   illustrated by equations a-e of Scheme 11.

Scheme 11

(a) RCO_2Na + $(CH_3)_3CCO_2CH_2Br$ → $RCO_2CH_2OCOC(CH_3)_3$
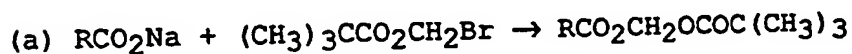
25

10   66

G. Francheschi et al., J. Antibiotics, 36, (7),
938-941 (1983).

30

47

$$\text{(b)} \quad RCO_2 + (CH_3)_2NCON(CH_3)_2 + Cl\overset{\overset{\displaystyle CH_3}{|}}{C}HOCOC(CH_3)_3$$

$$\downarrow$$

$$RCO_2\overset{\overset{\displaystyle CH_3}{|}}{C}HOCOC(CH_3)_3$$

67
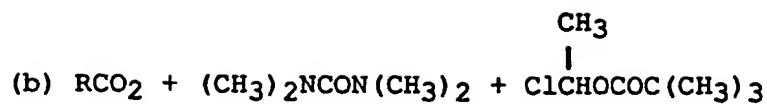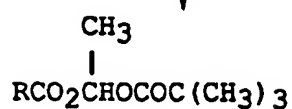
J. Budavin, U.S. Patent 4,440,942

$$\text{(c)} \quad RCO_2H \rightarrow RCO_2\overset{\overset{\displaystyle R^{24}}{|}}{C}H-OCOC\overset{\overset{\displaystyle}{|}}{\underset{\underset{\displaystyle NH_2}{|}}{H}}CH_2CO_2CH_3$$

68
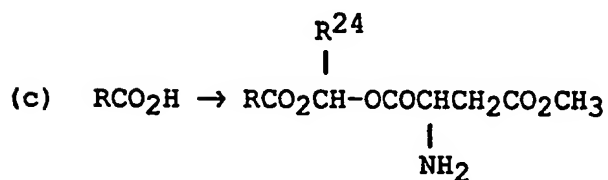
B. Daehne et al., G.B. Patent 1,290,787

$$\text{(d)} \quad RCO_2H \rightarrow RCO_2\overset{\overset{\displaystyle R^{24}}{|}}{C}HCONR^{22}R^{23}$$

69
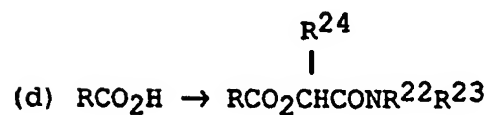
Ferres, Chem. Ind., 435-440 (1980)

(e) $R-CO_2H$ $\longrightarrow$

70

48
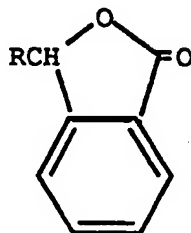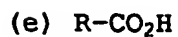
Clayton et al., _Antimicrob. Agents Chemotherapy_,
_5_, (6), 670-671 (1974)

In equations a-e: R =
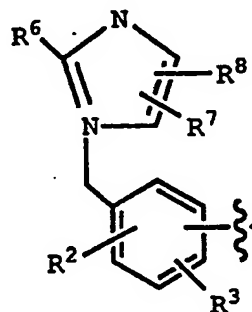
5

Compounds of Formula I where R^1 is $-C(CF_3)_2OH$
may be prepared as shown in Scheme 12.

Scheme 12

10

_71_   _72_
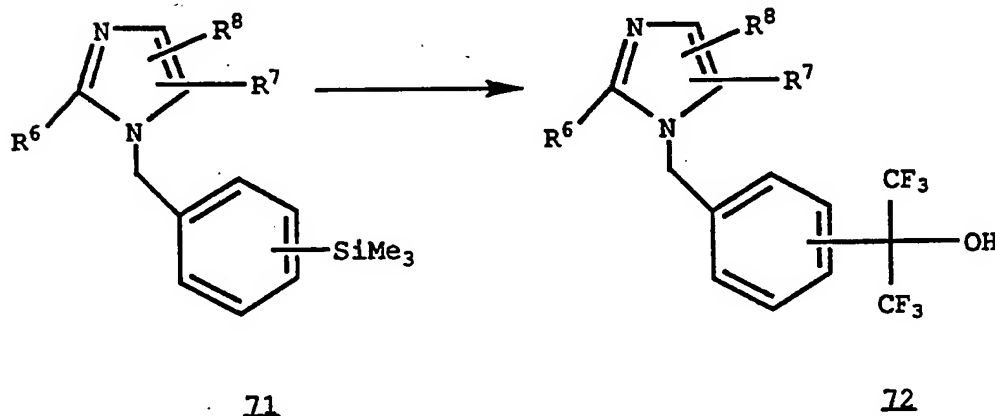
Hexafluoroisopropanol compounds (_72_) may be
prepared by treatment of arylsilane (_71_) with 1-5
15   equivalents of hexafluoroacetone in a solvent such as
methylene chloride at temperatures ranging from about
-50° to 25°C for a period of 2-10 hours. The requisite
arylsilane (_71_) can be prepared using methods known to
one skilled in the art such as the procedures described
20   in Chapter 10 of Butterworth's "Silicon in Organic
Chemistry".

Scheme 13

3a

63

73

[H]
reductive
amination

75

74

(R²³ ≠ H)

76   z =

77   z =

78   z =
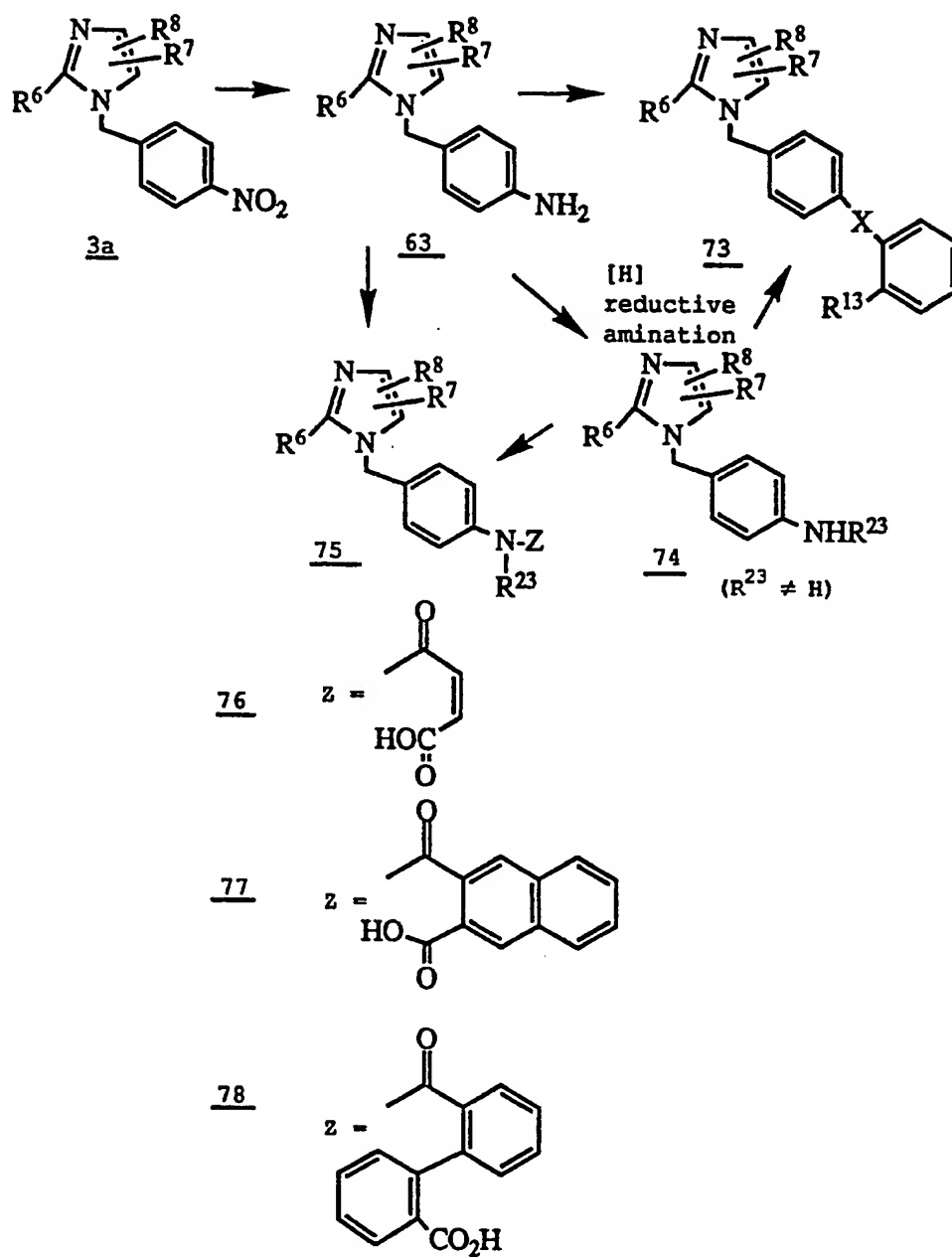
As shown in Scheme 13, compound (73) in which
X = -NHCO- and R^{13}= -COOH may b easily prepared, for
example, by reacting aniline precursor (63) with a
phthalic anhydride derivative in an appropriate solvent
5 such as benzene, chloroform, ethyl acetate, etc. Often
the carboxylic acid product will precipitate from
solution with the reactants remaining behind, M.L.
Sherrill, F.L. Schaeffer, E.P. Shoyer, J. Am. Chem.
Soc., 50, 474 (1928).
10 When R^{13}=NHSO$_2$CH$_3$, NHSO$_2$CF$_3$ or tetrazolyl (or a
variety of other carboxylic acid equivalents), compound
(73) may be obtained by reacting aniline (63) with the
requisite acid chloride by either a Schotten-Baumann
procedure, or simply stirring in a solvent such as
15 methylene chloride in the presence of a base such as
sodium bicarbonate, pyridine, or triethylamine.
Likewise, aniline (63) may be coupled with an
appropriate carboxylic acid via a variety of amide or
peptide bond forming reactions such as DCC coupling,
20 azide coupling, mixed anhydride synthesis, or any other
coupling procedure familiar to one skilled in the art.
Aniline derivatives (63) will undergo reductive
amination with aldehydes and ketones to form secondary
amines (74). Thus the aniline is first stirred with the
25 carbonyl compound in the presence of a dehydration
catalyst such as molecular sieves or p-toluenesulfonic
acid. Afterwards the resultant imine is reduced to the
amine with a borohydride reducing agent such as sodium
cyanoborohydride or sodium borohydride. Standard
30 catalytic hydrogenation reagents such as hydrogen and
palladium/carbon can also be employed.
Alternatively, aniline (63) may be monoalkylated by
reaction with ethyl formate followed by reduction with,
for example, lithium aluminum hydride to produce the
35 N-methyl derivative (74). Anilines (74) may in turn be

reacted with carboxylic acid anhydrides and acid
chlorides or carboxylic acids by any of the coupling
procedures described previously to yield (73) where X =
-N(CH$_3$)CO-.

5   Aniline (63) or (74) or other intermediate anilines
where the amino group may be located on another aromatic
ring for example, also react with other anhydrides to
make amide-carboxylic acid derivatives of formula (75).
Thus, for example, maleic anhydride, 2,3- naphthalene-
10   dicarboxylic acid anhydride, and diphenic anhydride are
reacted in a similar fashion to phthalic anhydride with
aniline (63) or (74) to yield carboxylic acids (76),
(77), and (78), respectively.

        Phthalimide derivatives of aniline (63) may be made
15   by a variety of methods, preferably by stirring aniline
(63) with phthalic anhydride in acetic acid at a
temperature between 20°C and reflux, G. Wanag,
A. Veinbergs, Ber., 75, 1558 (1942), or by stirring (63)
with phthaloyl chloride, a base such as triethylamine,
20   and an inert solvent.

        Aniline (63) may be converted into its trifluoro-
methanesulfonamide derivative or its trifluoroacetamido
derivative preferably by reacting it with triflic
anhydride or trifluoroacetic anhydride and a base such
25   as triethylamine in an inert solvent such as methylene
chloride at -78°C followed by warming to room
temperature.

        Compounds of structure (I) where X is a carbon-
carbon linkage which are depicted as (80) can be made as
30   shown in Scheme 14.

52

Scheme 14

Y = Cl, Br, OTs, OMs

a)

b)

halogenation

Y = Br, Cl

c)

d)

$R^1=CH_3$, Et, t-Bu, etc.

Scheme 14 (continued)

e) [structure: toluene with MgX] + ZnCl₂ → [structure: toluene with ZnCl]

Br [structure with CN] —Ni (II)→ [structure: —Ni— with CN]

→ [biphenyl structure with CH₃ and CN] —H+→ **88**
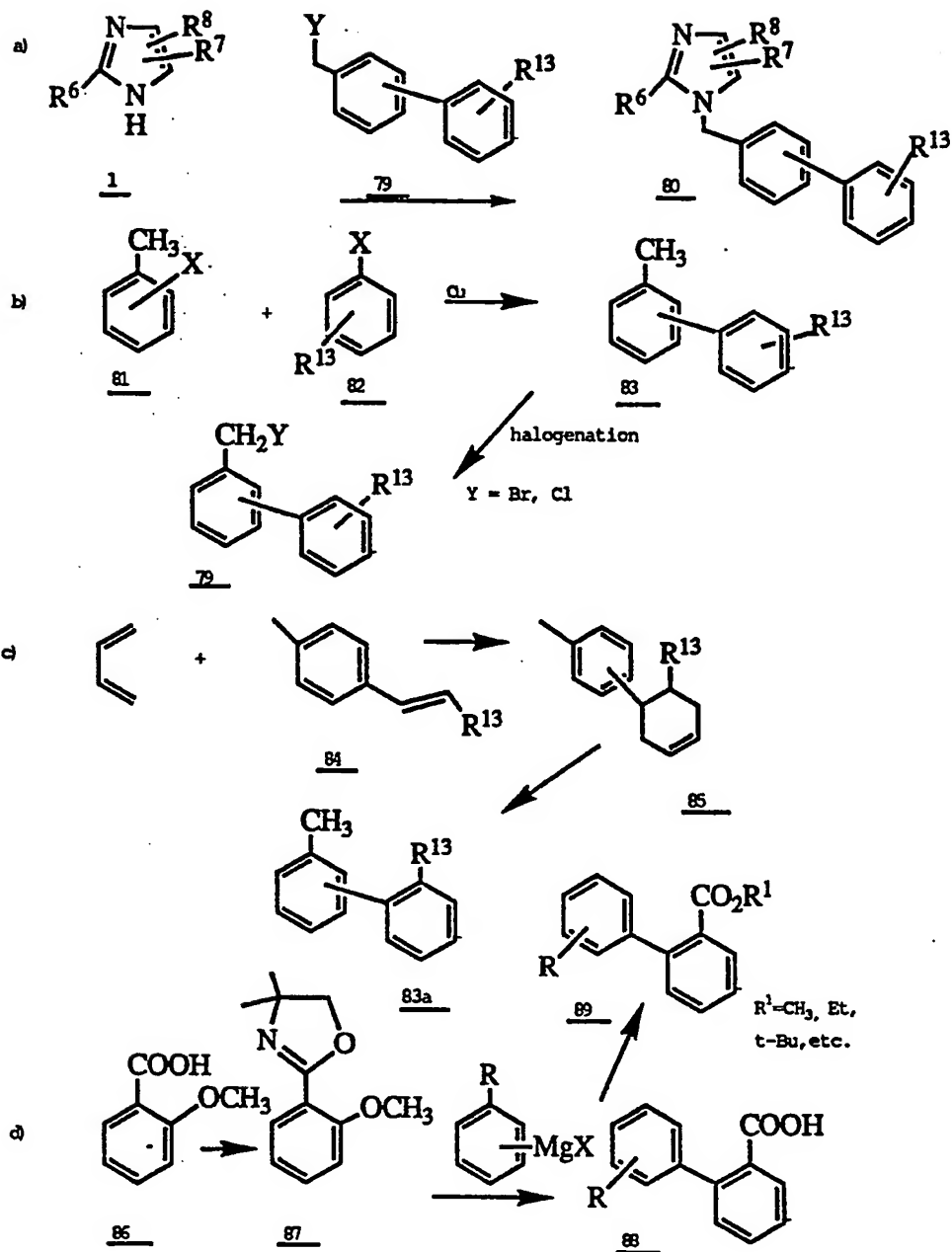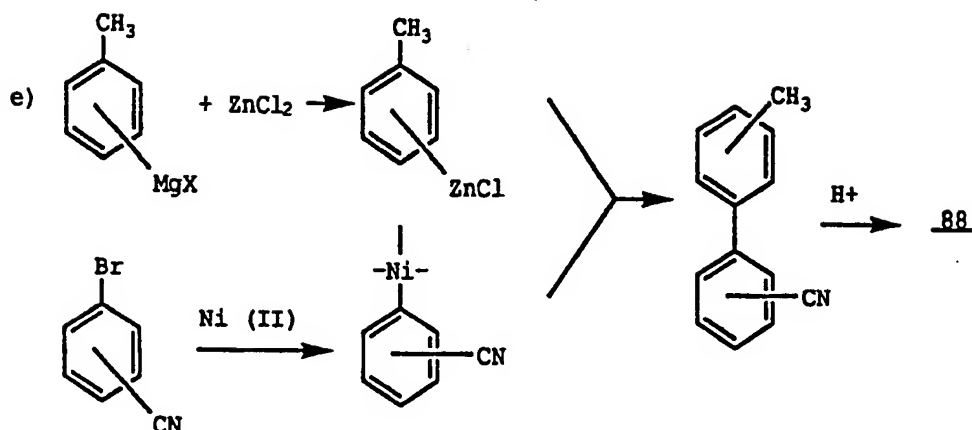
Equation a) illustrates that the biphenyl compounds
(**80**) can be prepared by alkylation of imidazole (**1**) with
5   the appropriate halomethylbiphenyl compound (**79**) by the
general procedure described in Scheme 1.

The requisite halomethylbiphenyl intermediates (**79**)
are prepared by Ullman Coupling of (**81**) and (**82**) as
described in "Organic Reactions", 2, 6 (1944) to provide
10 intermediates (**83**), which are in turn halogenated.
Halogenation can be accomplished by refluxing (**83**) in an
inert solvent such as carbon tetrachloride for 1-6 hours
in the presence of a N-halosuccinimide and an initiator
such as azobisisobutyronitrile (equation b).

15   As shown in equation c), derivatives of inter-
mediate (**83**) in which R^{13} is at the 2' position (**83a**)
can also be prepared by the method described in J. Org.
Chem., 41, 1320 (1976), that is Diels-Alder addition of
a 1,3-butadiene to a styrene (**84**) followed by
20 aromatization of intermediate (**85**).

Alternatively, the substituted biphenyl precursors
(**83**; where R^{13} = COOH) and their esters (**89**) can be
prepared as illustrated in equation d), which involves

54

oxazoline compounds as key intermediates, A. I. Meyers
and E. D. Mihelich, *J. Am. Chem. Soc.*, *97*, 7383 (1975).

Further, as shown in Equation e), nickel-catalyzed
cross-coupling of an arylzinc halide with a

5   halobenzonitrile yields a biphenylnitrile which can in
turn be hydrolyzed by standard methods to afford acid
88.

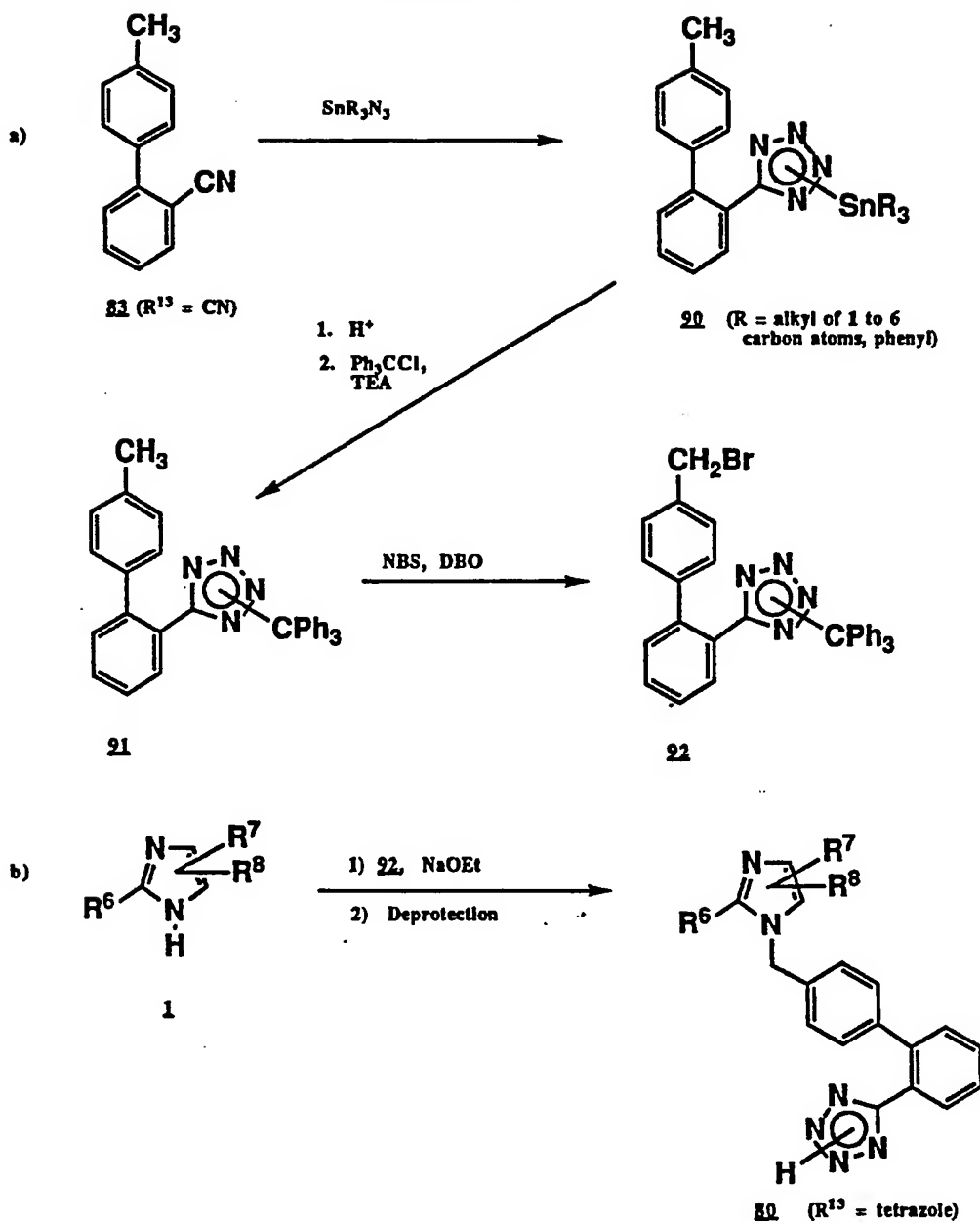The substituted biphenyl tetrazoles (83; where

$$R^{13} = N\begin{smallmatrix} N==N \\ \diagup \quad \diagdown \\ N \quad\quad NH \end{smallmatrix})$$

10   can be prepared from the nitrile
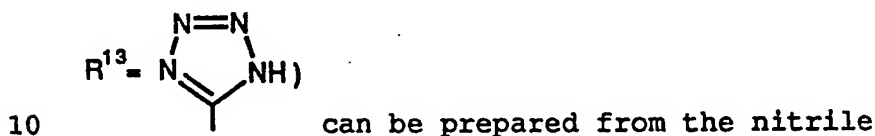
precursors (R^{13}=CN) by the methods described in
Scheme 1, equation c) and Scheme 15, equation c).

However, a preferred method for preparing
15   tetrazoles is described in Scheme 15, equations a) and
b). Compounds (90) may be prepared by the 1,3-dipolar
cycloaddition of trialkyltin or triphenyltin azides to
the appropriately substituted nitrile (83) as in
equation a). Alkyl is defined as normal alkyl of 1-6
20   carbon atoms and cyclohexyl. An example of this
technique is described by S. Kozima, et al., *J.*
Organometallic Chemistry, 337 (1971). The required
trialkyl or triaryltin azides are made from the
requisite commercial trialkyl or triaryl tin chloride
25   and sodium azide. The trialkyl or triaryltin group is
removed via acidic or basic hydrolysis and the tetrazole
can be protected with the trityl group by reaction with
trityl chloride and triethylamine to give (91).
Bromination as previously described herein with
30   N-bromosuccinimide and dibenzoylperoxide affords
compound (92). Alkylation of (1) with the appropriately
substituted benzyl halide using conditions previously
described followed by deprotection of the trityl group

via hydrolysis affords (80; R^{13} = tetrazole). Other
protecting groups such as p-nitrobenzyl and
1-ethoxyethyl can be us d instead of the trityl group to
protect the tetrazole moiety. These groups as well as

5   the trityl group can be introduced and removed by
procedures described in Greene, _Protective Groups in
Organic Synthesis_, Wiley-Interscience, (1980).

Scheme 15

a)

$\underline{83}$ (R^{13} = CN)

SnR$_3$N$_3$

$\underline{90}$ (R = alkyl of 1 to 6 carbon atoms, phenyl)

1. H$^+$
2. Ph$_3$CCl, TEA

$\underline{91}$

NBS, DBO

$\underline{92}$

b)

$\underline{1}$

1) $\underline{92}$, NaOEt
2) Deprotection

$\underline{80}$ (R^{13} = tetrazole)

57
Scheme 15 (continued)

c)

83

83a
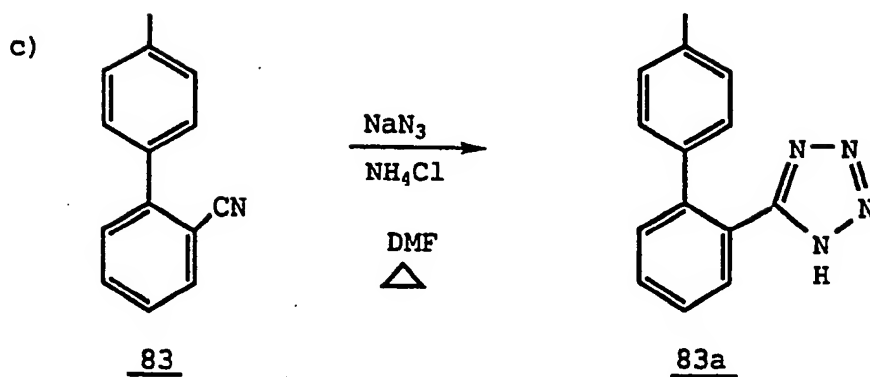
Compounds of structure 93-95 where X is an
-O-, -S-, or -N- linkage can be prepared as shown
$\overset{|}{R}26$

in Scheme 16 by alkylation of imidazole (1) with the
appropriate benzyl halide (96).

58

Scheme 16

a)

93; X = O
94; X = S
95; X = NR²⁶

b)

97-100

101-104

97; X = O
98; X = S
99; X = NH
100; X = NR²⁶ (R²⁶ ≠ H)

109; X = O
110; X = S
111; X = NH
112; X = NR²⁶ (R²⁶ ≠ H)

105-108

109-112
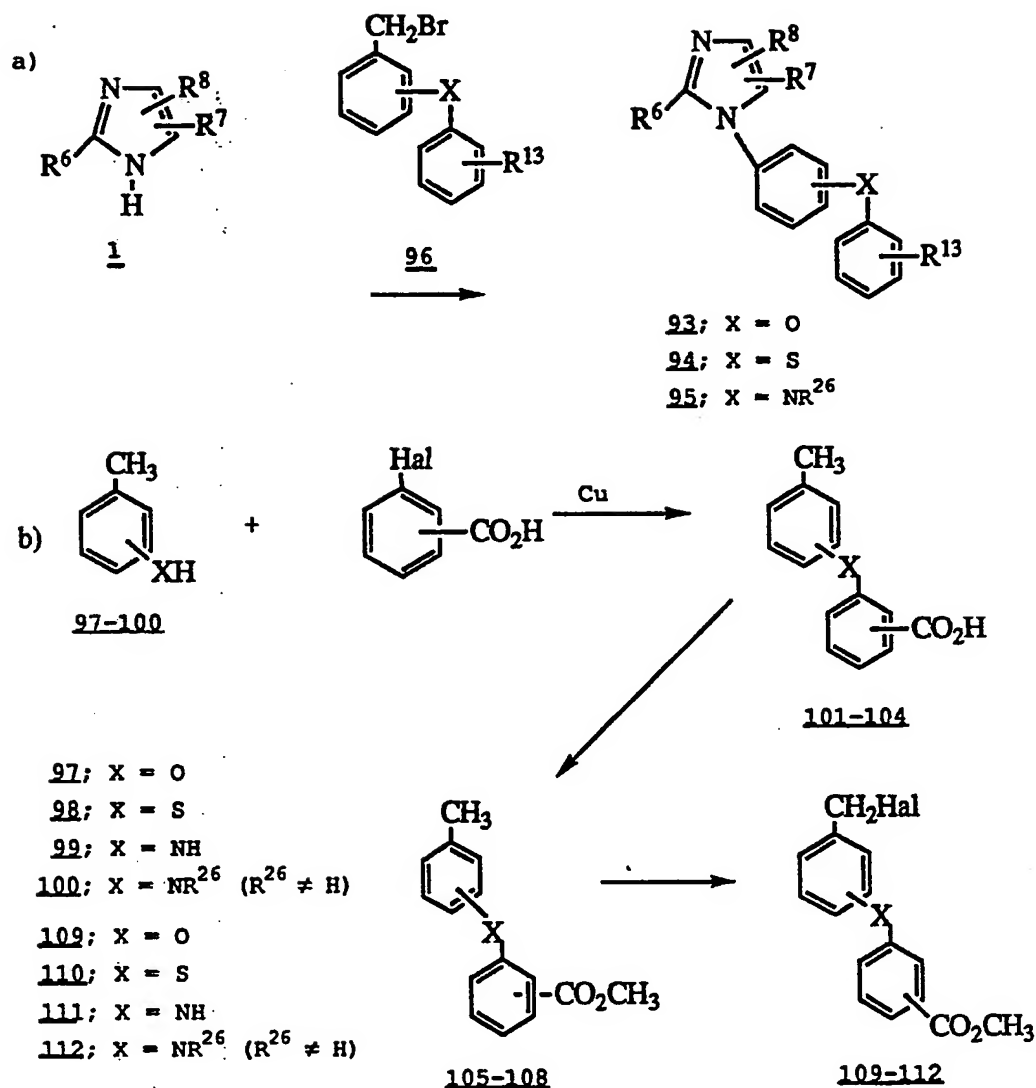
5   The halomethyldiphenyl ether (109) employed as an
alkylating agent in the present invention is prepared as
shown in equation b). An Ullman ether condensation of
the phenol (97) and a halobenzoic acid as described in
Russian Chemical Reviews, 43, 679 (1974) provides the
10   intermediate acid (101). The conversion of (101) into
(109) is accomplished by esterification with
diazomethane to afford (105) followed by halogenation

59

employing the procedure used in the pr paration of (79).
The diphenylsulfide (110) and the diphenylamine (111)
can be prepared from the appropriate thiophenol (98) or
aniline (99) by this procedure.

5   The tertiary diphenylamine (112) can be prepared
from the secondary aniline (100) by the above procedure.
Alternatively (107) can be alkylated by one of the
following procedures: 1) direct alkylation of (107) with
$R^{26}L$ where L is a leaving group such as a halogen or

10   tosylate employing phase-transfer conditions and
ultrasound as described in Tetrahedron Letters, 24, 5907
(1983), 2) treatment of (107) with 1-1.5 equivalents of
an appropriate aldehyde and 0.5-5.0 equivalents of
sodium cyanoborohydride in a solvent such as methanol at

15   25°C at a pH of 3-6 for 1-24 hours, or 3) reductive
amination of (107) employing an appropriate carboxylic
acid and sodium borohydride as described in J. Am. Chem.
Soc., 96, 7812 (1974). The tertiary amine (108) is then
halogenated by the procedure previously described to

20   give (112).

60

Scheme 17
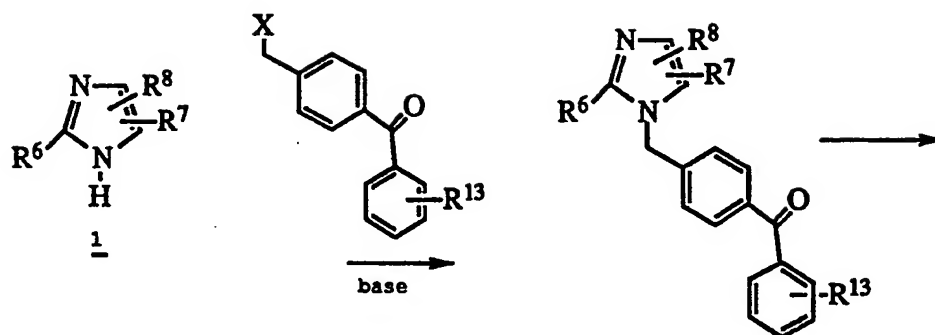
114; $R^{13} = 2-CO_2CH_3$, X = halide
115; $R^{13} = 2-CO_2CH_3$, X = H

73a
113, $R^{13} = 2-CO_2CH_3$
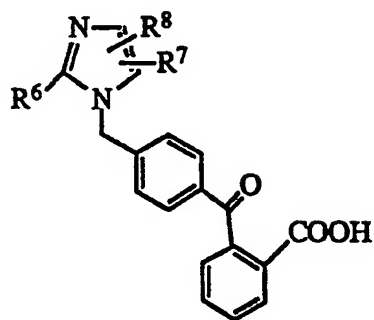
116

Compounds of structure (73) where X is -CO- are prepared as shown in Scheme 17 by alkylation of imidazole (1) with the requisite benzoylbenzyl halides. For example, esters (113) where R^{13} is 2-CO_2CH_3 are

5   prepared by alkylation of imidazole (1) with carbomethoxybenzoyl benzyl halide (114). Ester (113) may be hydrolyzed to the corresponding carboxylic acid (116) by a variety of methods including hydrolysis with a base such as sodium hydroxide or potassium hydroxide

10 in an alcoholic aqueous solvent such as methanol/H_2O at a temperature from 20°C to the reflux temperature of the solvent.

Carboalkoxybenzoylbenzyl halides (114) are prepared by benzylic halogenation of the corresponding

15 toluoylbenzene precursor by a variety of methods previously described herein. For example, methyl 2-(4-methylbenzoyl)benzoate (115) can be refluxed for 2-48 hours with N-bromosuccinimide, benzoyl peroxide and carbon tetrachloride to effect benzylic bromination.

20

62

Scheme 18

117

73a (where X = CO)

118

[H]

119

121

120

122

123
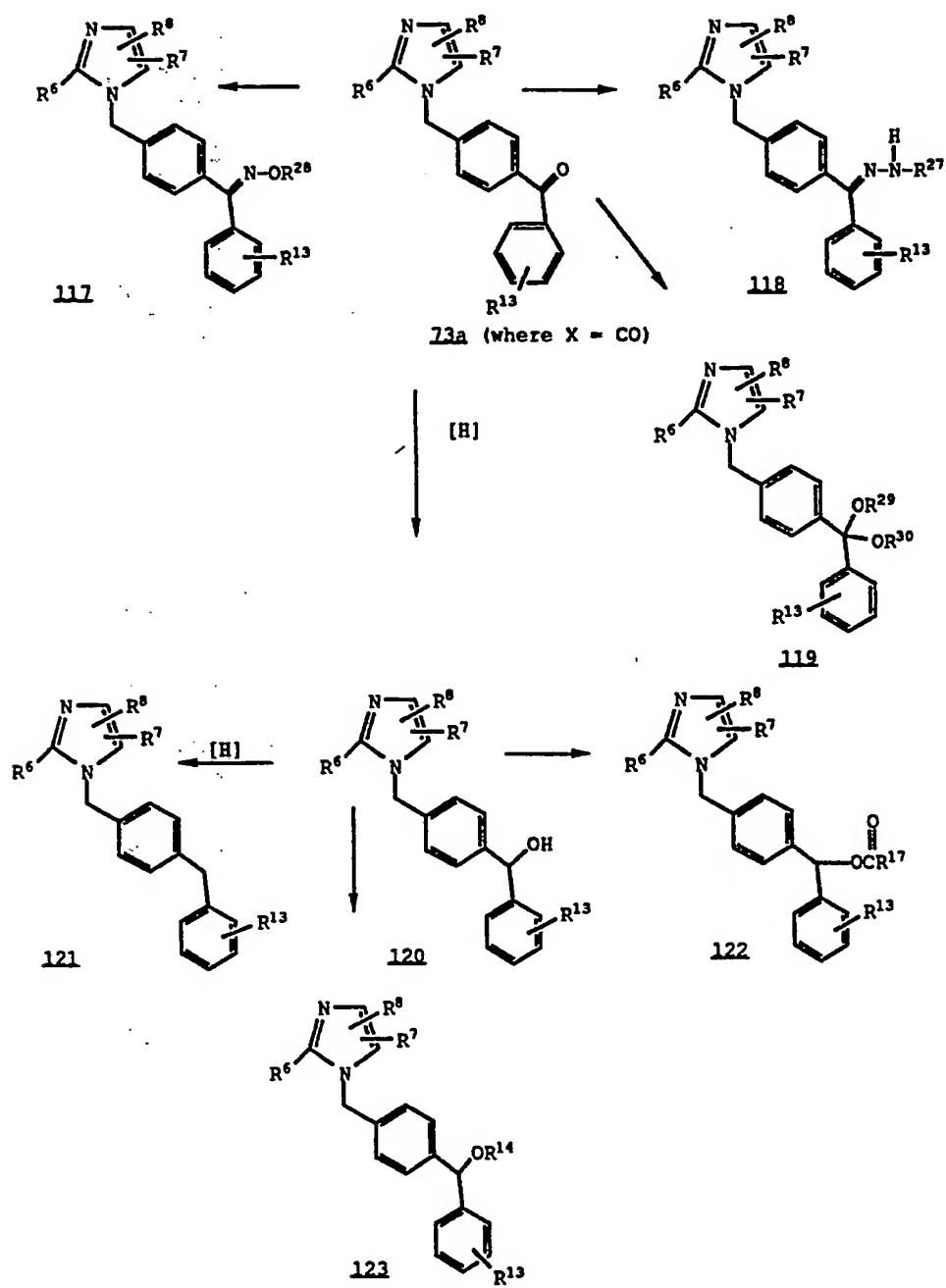
As shown in Scheme 18 the toluoyl ketones (73;
where X = CO) may be further transformed into a variety
of ketone derivatives including compounds where X is

5

$$\underset{-C-}{\overset{NR^{25}}{\overset{\|}{}}},\qquad \underset{-C-}{\overset{R^{29}\ O}{\overset{\backslash\,/}{}}},\quad \underset{-CH}{\overset{OR^{30}}{\overset{|}{}}},\quad \text{and}\ \underset{-C-}{\overset{OR^{14}}{\overset{|}{}}}.$$
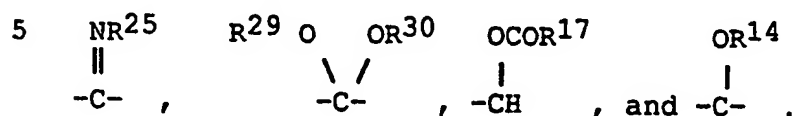
Reaction of ketone (73a) with a hydroxylamine or an
10 appropriately substituted hydrazine will give the
requisite oximes (117) and hydrazones (118). Reaction
with alcohols in the presence of an acidic catalyst with
removal of water will give ketals (119). Reduction,
with lithium aluminum hydride, a metal borohydride,
15 zinc/acetic acid or catalytic hydrogenation will give
the corresponding alcohol (120) or fully reduced
methylene compound (121). These alcohols may be
acylated by a variety of anhydrides or acid halides in
the presence of a base with or without solvent to give
20 the corresponding esters (122). The alcohols (120) may
be converted into their corresponding ethers (123) by
reaction of the metal alkoxide with an alkyl halide,
mesylate or tosylate in the appropriate solvent or by
treatment with a mineral acid in an alcoholic solvent,
25 or by reaction of the alcohol with diazomethane as
described in G. Hilgetag and A. Martini, "Preparative
Organic Chemistry", John Wiley, New York, 355-368
(1972).

Compounds of formula (I) where X is $-OCH_2-$,
30 $-SCH_2-$, and $-NHCH_2-$ are prepared as shown in Scheme 19.

64

Scheme 19

a)

    124; R = CH₂Ph
    125; R = CH₃

b)

c)
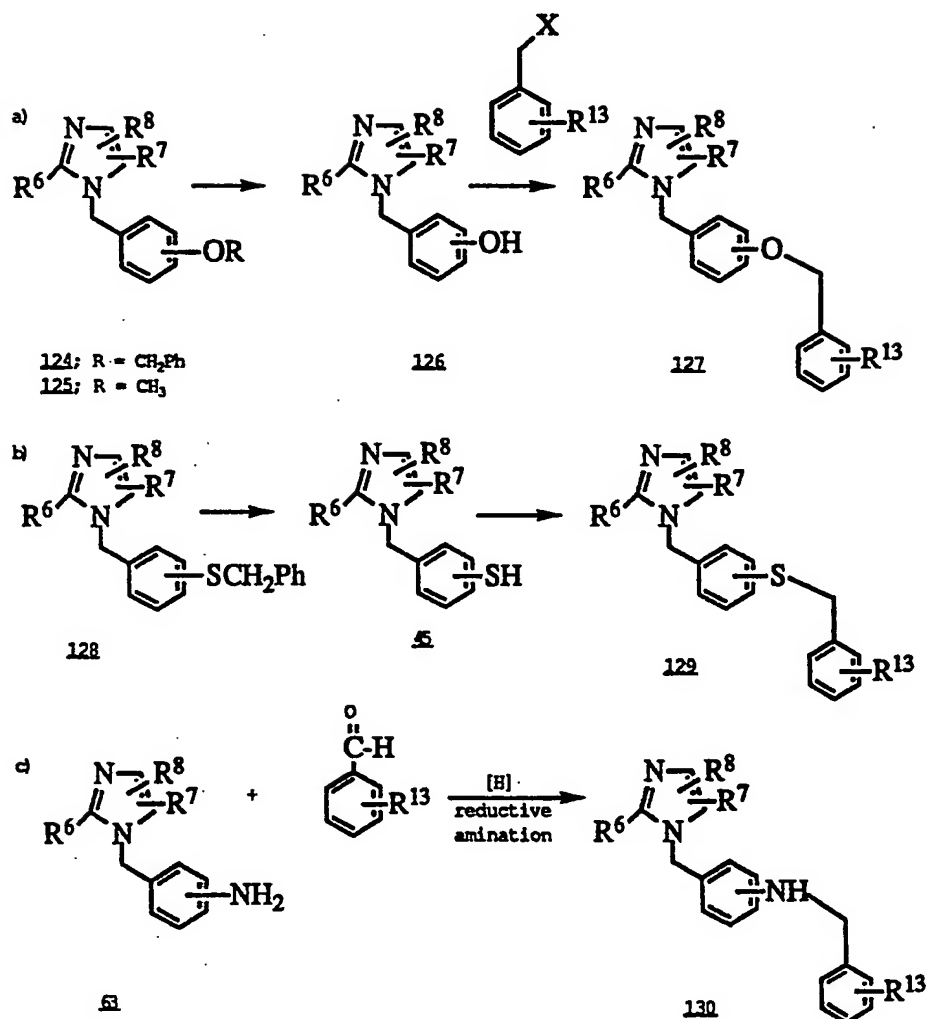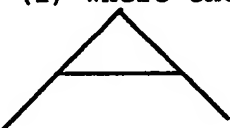
5   As illustrated in Scheme 19, equation a, hydrolysis
    of benzyl ether (124) or methyl ether (125) affords
    hydroxy compound (126) which can be alkylated with the
    appropriate benzyl halide to give (127). In the case of
    the methyl ethers (125), the hydrolysis step can be
10   effected by heating the ether at temperatures of
    50°-150°C for 1-10 hours in 20-60% hydrobromic acid, or
    heating at 50°-90°C in acetonitrile with 1-5 equivalents
    of trimethylsilyl iodide for 10-50 hours followed by
    treatment with water. Hydrolysis can also be carried

out by treatment with 1-2 equivalents of boron
tribromide in methylene chloride at 10°-30°C for 1-10
hours followed by treatment with water, or by treatment
with an acid such as aluminum chloride and 3-30

5   equivalents of a sulfur-containing compound such as
thiophenol, ethanedithiol, or dimethyl disulfide in
methylene chloride at 0-30°C for 1-20 hours followed by
treatment with water. For compound (124), hydrolysis
can be accomplished by refluxing in trifluoroacetic acid

10 for 0.2-1 hours or by catalytic hydrogenolysis in the
presence of a suitable catalyst such as 10% palladium on
carbon. Deprotonation of (126) with a base, such as
sodium methoxide, sodium hydride or the like in a
solvent such as dimethylformamide or dimethylsulfoxide

15 at room temperature followed by alkylation with an
appropriate benzyl halide at 25°C for 2-20 hours affords
ethers of formula (127), as shown in equation a.

The sulfide (129) can be prepared from the
thiophenol (45) by the procedure described above to

20 prepare the ether (127) from the phenol (126). The
thiophenol (45) can be prepared for example by treatment
of the benzylsulfide (128) with sodium in liquid
ammonia.

The amine (130) can be prepared as shown in

25 equation c, from the aniline (63), itself available from
reduction of the corresponding p-nitro compound (3a)
which has previously been described. The reductive
amination can be carried out by the same procedure as
described in Scheme 13 for the preparation of compound

30 (74).

Compounds of Formula (I) where the X linkage is

-CH=CH-, -CH2CH2-, and   are prepared as
shown in Scheme 20.

Scheme 20
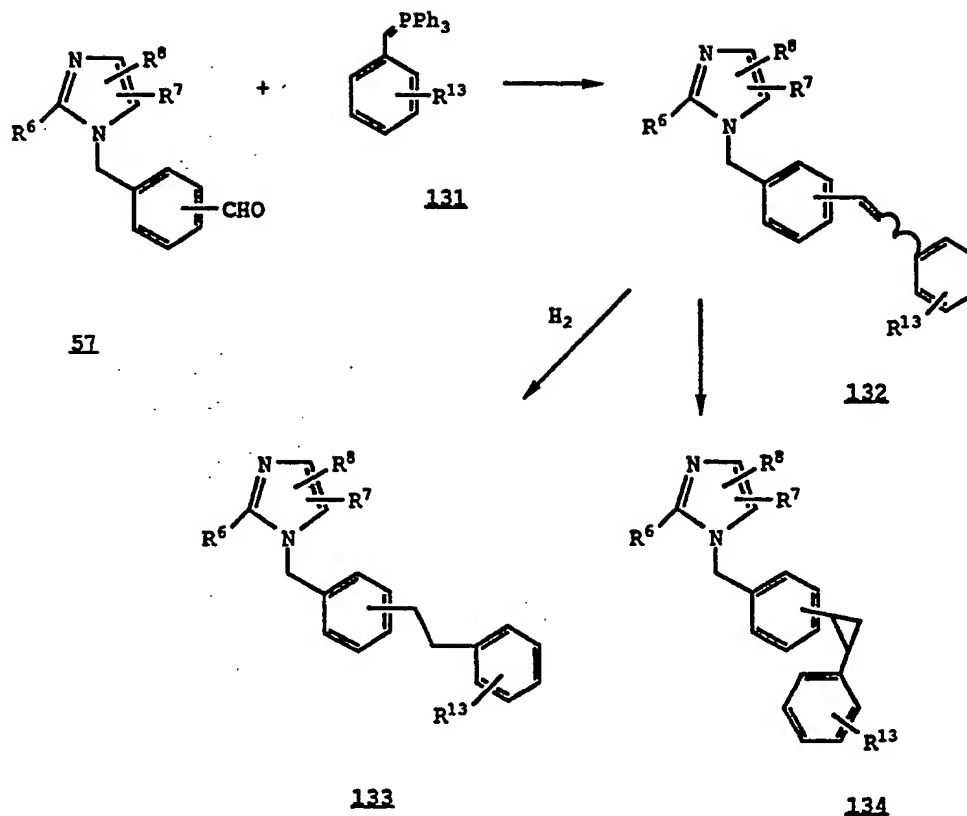
The cis or trans stilbene (132) can be obtained by
employing a Wittig reaction between the aldehyde (57)
and the phosphorane (131).

The stilbene (132) can readily be converted to the
10   saturated derivative (133) for example ·by catalytic
hydrogenation employing a heterogeneous catalyst such as
palladium/carbon or platinum/carbon or alternatively
with a homogeneous catalyst such as tristriphenylphos-
phine rhodium chloride. The reduction is performed in a
15   solvent such as benzene, tetrahydrofuran or ethanol at
25°C under 1-3 atmospheres of hydrogen for 1-24 hours.

The cyclopropane (134) can be prepared by treating
the stilbene (132) with the Simmons-Smith reagent as

described in _J. Am. Chem. Soc._, **81**, 4256 (1959), or by
treating (**132**) with methylene diiodide and copper powder
as described in _J. Am. Chem. Soc._, **101**, 2139 (1979),
or by treatment with the iron-containing methylene
5   transfer reagent described in _J. Am. Chem. Soc._, **101**,
6473 (1979).

The preparation of compounds of formula (I) where X
is $-CF_2CH_2-$, $-CF=CH-$, $-CH=CF-$, $-CF=CF-$ and $-CF_2CF_2-$ are
depicted in _Scheme 21_.

68

Scheme 21

a) $\overset{\overset{\displaystyle O}{\|}}{ArCCH_2Ar'}$ + Et_2NSF_3 $\xrightarrow{CH_2Cl_2}$ $ArCF_2CH_2Ar'$

<u>135</u> $\searrow$ THF, H^+ <u>136</u>

                                              $\swarrow$ Al_2O_3

                    $ArCF = CHAr^1$

                         <u>137</u>

b) $\overset{\overset{\displaystyle O}{\|}}{ArCH_2CAr'}$ + Et_2NSF_3 $\xrightarrow{CH_2Cl_2}$ $ArCH_2CF_2Ar'$

<u>138</u> $\searrow$ THF, H^+ <u>139</u>

                                              $\swarrow$ Al_2O_3

                    $ArCH = CFAr^1$

                         <u>140</u>

c) $\overset{\overset{\displaystyle O \quad OH}{\| \quad |}}{ArCCHAr'}$ + Et_2NSF_3 $\xrightarrow{CH_2Cl_2}$ $ArCF_2CHFAr'$

<u>141</u> $\searrow$ THF, H^+ <u>142</u>

                                              $\swarrow$ Al_2O_3

                    $ArCF = CFAr^1$

                         <u>143</u>

d) $\overset{\overset{\displaystyle O \; O}{\| \; \|}}{ArCCAr'}$ + Et_2NSF_3 $\longrightarrow$ $ArCF_2CF_2Ar'$

<u>144</u>   <u>145</u>
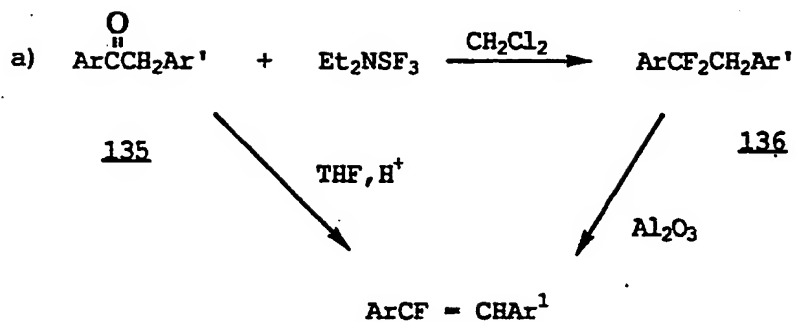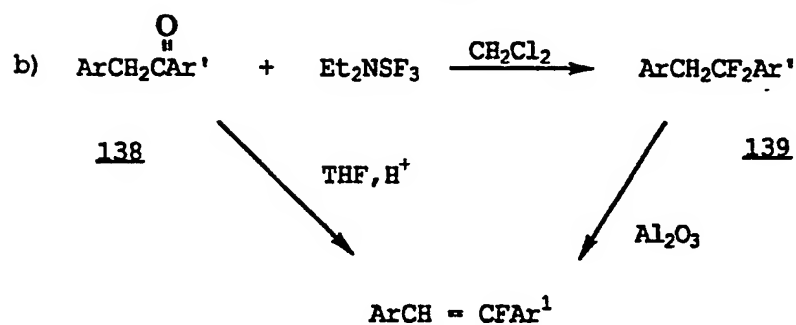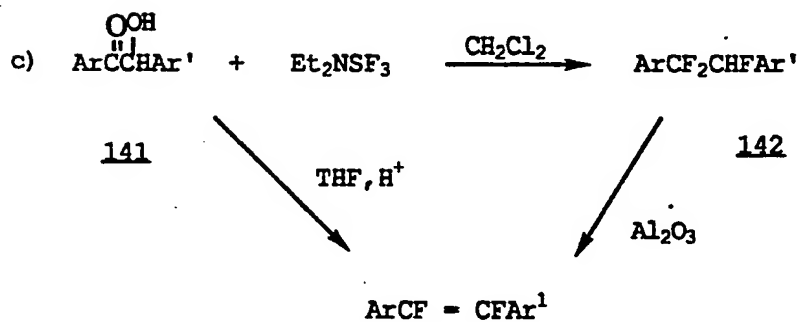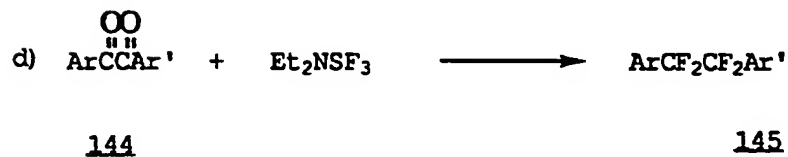
Vinylene fluorides (137) and (140) can be prepared
by reaction of SF$_4$ or Et$_2$NSF$_3$ (DAST) with the
appropriate ketone (135) or (138) in which Ar bears a
methyl group convertible to a benzylic halide suitable

5   for attachment to an imidazole nitrogen, and Ar' bears a
cyano, nitro, ester, or other suitable group which can
be subsequently converted to CO$_2$H, NHSO$_2$CF$_3$, etc. The
initially formed difluoroethylene (136) and (139) can be
formed in a non-polar solvent such as methylene chloride

10   and subsequently converted to the vinylene fluoride by
means of alumina, or converted directly into the
unsaturated fluoride by running the reaction in a polar
solvent such as tetrahydrofuran, diglyme or N-
methylpyrrolidone in the presence of mineral acid.

15   [Equations a and b]. Experimental details of such
procedures are found in D.R. Strobach and G.A. Boswell,
J. Org. Chem., 36, 818 (1971); G.A. Boswell, U.S.
Patents 3,413,321 (1968) and 4,212,515 (1980).

As shown in equation c) an appropriate benzoin

20   (141) may be similarly converted to the corresponding
1,2-difluorostilbene (143). Likewise as shown in
equation d) an appropriate benzil (144) can be converted
to a tetrafluorodiarylethylene (145) using DAST or SF$_4$.
Experimental details are described in M.E. Christy, et

25   al., J. Med. Chem., 20, (3), 421-430, (1977).

$$R^{23}$$
$$|$$
Compounds of formula 1 where X = -CON-, -CH$_2$O-,
30   -CH$_2$S-, -CH$_2$NH-, can be made as shown in Scheme 22.

Scheme 22

a)

R^{23}

$HN-ArR^{13}-P$ (146)

DCC, CH_2Cl_2

or

R^{23}

$HN-ArR^{13}, TsCl, pyr$

P

10

147

deprotection
if necessary

148

P = protecting group (if necessary)

$ArR^{13} =$, $ArR^{13} =$

$ArR^{13} =$

b)

149

150

TsCl
pyr

151

K_2CO_3, DMF

deprotection

152: $HO-Ar-R^{13}-P$

153: $HS-Ar-R^{13}-P$

146: $H_2N-Ar-R^{13}-P$

154: X = $-CH_2O-$

155: X = $-CH_2S-$

156: X = $-CH_2NH-$

71
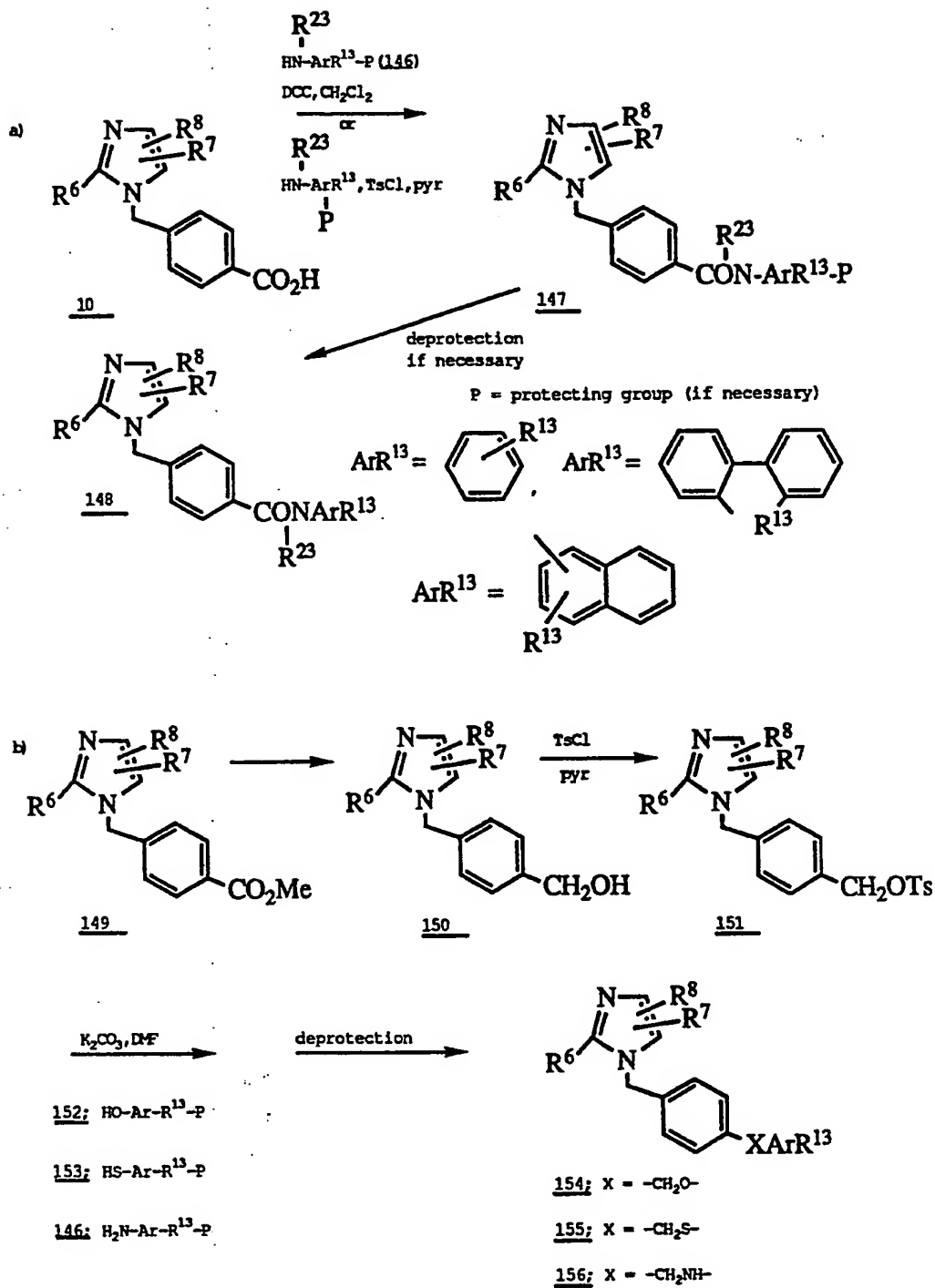
As previously described, acid (10) can be made by
alkylating the appropriate imidazole with methyl
4-chloromethylbenzoate in the presence of a base such as
potassium carbonate in a polar solvent such as
5   dimethylformamide followed by hydrolysis of the
resulting ester. Compound (10) can be converted to
(148) by reaction with the requisite amine (146) (R^{13}
may need to be protected and subsequently deprotected)
and dicyclohexyl carbodiimide (DCC) in methylene
10   chloride [J. R. Beek, et al., _J. Am. Chem. Soc_, _90_, 4706
(1968)] or by reaction with tosyl chloride in pyridine
[J. H. Brewster and C. J. Ciotti, Jr., _J. Am. Chem.
Soc._, _77_, 6214 (1955)]. Yet another process involves
conversion of carboxylic acid (10) to its acid chloride
15   with, for example, thionyl chloride followed by reaction
with the amine in aqueous base (Schotten–Baumann
conditions) or in an organic solvent in the presence of
an acid scavenger such as $NaHCO_3$, pyridine or
triethylamine, or by other procedures known to form an
20   amide bond between an aromatic acid and an amine.

The compounds where X= $-CH_2O-$, $-CH_2S-$, and $-CH_2NH_2-$
can be made as shown in pathway _b_. The ester (149) is
reduced with a reducing agent such as lithium aluminum
hydride in an inert solvent to form the alcohol (150)
25   which can then be reacted with tosyl chloride in
pyridine to form tosylate (151), which is in turn
reacted in the presence of base with a corresponding
phenol (152) thiophenol (153), or aniline (146; where
R^{23}=H) to form compounds (154), (155) or (156). Again
30   this may require that R^{13} be protected with a suitable
protecting group, however modifications necessary
because of specific functional groups are understood to
be incorporated by one skilled in the art of organic
synthesis.

72

Alternatively, the alcohol (150) can be converted
to the corresponding halide with $SOCl_2$, $(COCl)_2$, etc,
and the resulting halide can then be reacted with a
phenol, thiophenol or aniline in the presence of base to
5   form the desired compound, where X is $-CH_2O-$, $-CH_2S-$,
$-CH_2NH-$ respectively.

<u>Scheme 23</u>

a)

b)
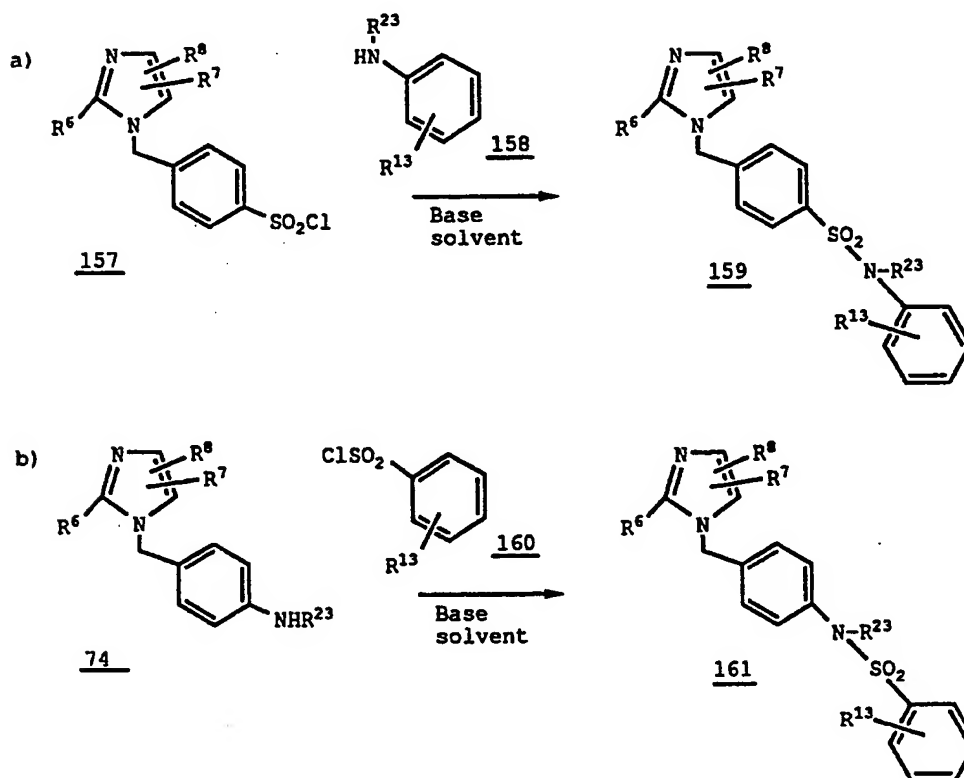
10

Compounds of Formula (I) where X= $-SO_2NR^{23}-$ and
$-NR^{23}SO_2-$ may be prepared as shown in <u>Scheme 23</u>. As
shown in equation a, sulfonylchloride derivative (157)
15   can be reacted with aniline derivative (158) in a
solvent in the presence of an acid scavenger such as
sodium bicarbonate, triethylamine or pyridine or under
Schotten-Baumann like conditions to give (159).
Sulfonylchloride derivative (157) can be obtained by

sulfonation of the corresponding benzyl derivative as
described earlier, followed by reaction with PCl_5 or
$POCl_3$. Likewise, aniline (74) may be reacted in the
same manner as described above with sulfonylchloride

5   derivative (160) to give (161).

Scheme 24 shows the preparation of furan analogs of
the biphenyl compounds (80). Thus, a-ketoester (162),
W. Wierenga and H. I. Skulnick, J. Org. Chem., 44, 310
(1979), or the corresponding nitrile (E=CN) can be

10 easily alkylated via standard procedures already
mentioned by an alkyl bromide derivative to give (163).
The alkene moiety of (163) can be subsequently cleaved
by oxidation, for example, with osmium tetroxide, Fieser
and Fieser, V.1, p. 812 (Lemieux-Johnson oxidation) to

15 yield dicarbonyl-containing compound (164). Cyclization
in mineral acids, acidic ion-exchange resin,
$POCl_3$/pyridine, or trifluoroacetic anhydride with a
catalytic amount of trifluoroacetic acid yields furan
(165; Z=O). Reaction of (164) with P_4S_{10}, for example,

20 will yield the corresponding thiophene (165; Z=S).
Reaction of (164) with an amine in refluxing benzene,
with azeotropic removal of water or by using molecular
sieves to absorb the water will yield the corresponding
pyrrole (165; Z=NR^{11}). Compounds (166) may be prepared

25 from (165) by standard procedures already described.

Scheme 24

Br (Cl, I, OTs, OMs, etc.)

162   E = CO$_2$CH$_3$ or CN

163

164

165

E = CO$_2$Me, CN
Z = O, S, NR^{11}

R^6

R^8

R^7

(COOH) or

N—N—N

N
H

166   Z = O, S, NR^{11}
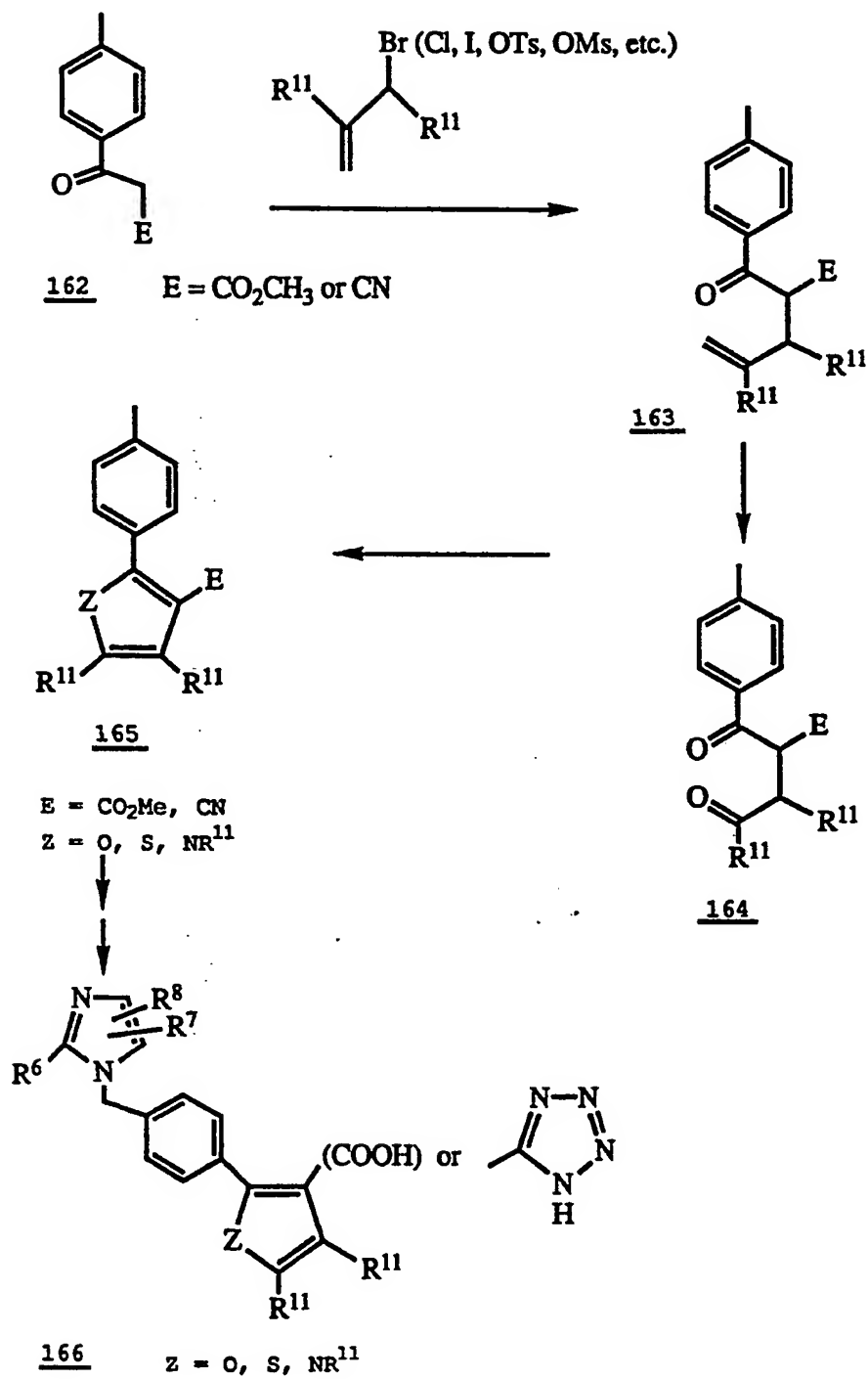
Compounds wherein a methylene group is inserted between the terminal aromatic ring and the acidic functionality may be prepared as shown in _Scheme 25_, equation a). Thus reduction of ester (_167_) with, for
5   example, lithium aluminum hydride, gives alcohol (_168_). Conversion of (_168_) to the chloride (_169_) via thionyl chloride followed by reaction with cyanide anion as previously described yields nitrile (_170_). Compound (_170_) may be hydrolyzed to carboxylic acid (_171_) by
10 methods already described or reacted with a hydrazoic acid equivalent to produce tetrazole (_172_).

Compounds wherein R^{13} is a trifluoromethylsulfonyl hydrazide acidic functional group were prepared by the procedure described in equation b). That is, conversion
15 of ester (_167_) to the hydrazide (_173_) by standard hydrazinolysis followed by reaction with triflic anhydride affords hydrazides (_174_).
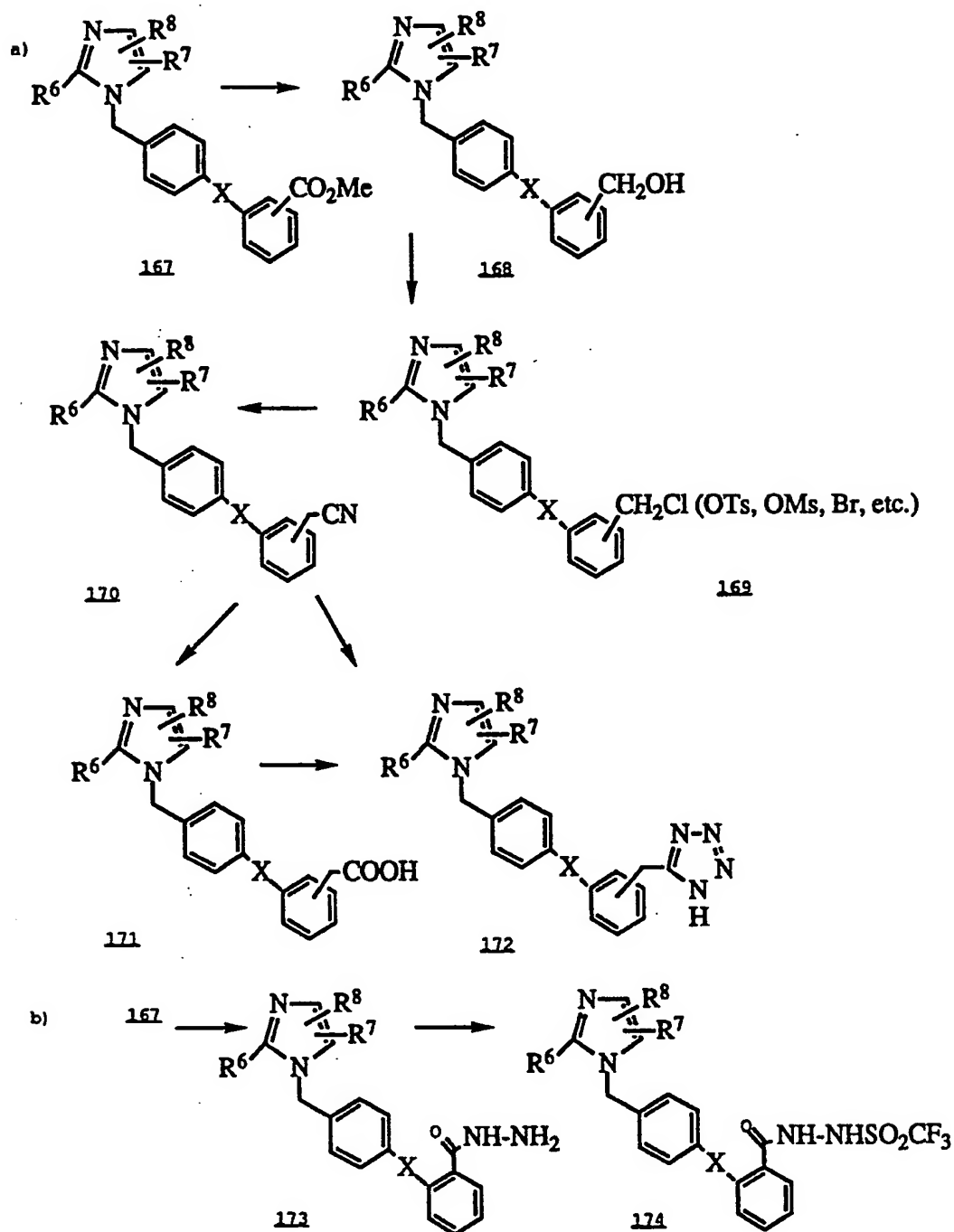
Scheme 25

5   The syntheses of compounds wherein R^{13} is
substituted and unsubstituted 1,2,3-triazoles are

described in Scheme 26. Thus reduction of ester (175)
with a reducing agent such as lithium aluminum hydride
or diisobutylaluminum hydride gives alcohol (176).
Oxidation with MnO_2 or pyridinium chlorochromate

5   converts (176) into aldehyde (177). Nitroethylene
derivative (178) is prepared by condensation of aldehyde
(177) with nitromethane in the presence of a catalyst,
R. M. Letcher and M. P. Sammes, J. Chem. Ed., 62, 262
(1985). Reaction of (178) with sodium azide produces

10 the 1,2,3-triazole (179), (N. S. Zefirov, et al.,
J. Chem. Soc. Chem. Comm., 1001 (1971)) which may be
transformed via procedures already described into
product (180).

Aldehyde (177) can also be converted into

15 substituted 1,2,3-triazoles (183) via the sulfone (181),
.G. Beck, D. Gunther Chem. Ber., 106, 2758 (1973),
followed by reaction with sodium azide to give the
1,2,3-triazole (182). Subsequent standard manipulations
lead to 1,2,3-triazoles (183) where E=CN and CO_2R^{11}.

20 The nitrotriazole (183; $E=NO_2$) may be synthesized from
the unprotected triazole (179; P=H) via nitration, R. Hu
ttel, et al., Chem. Ber., 88, 1586 (1955), C. L.
Habraken and P. Cohen-Fernandes J. Chem. Soc., 37
(1972), or from bromonitroethylene derivative (184), G.

25 Kh. Khisamutdinov, et al., Zh. Org. Khim., 11, 2445
(1975), by reaction with sodium azide.

A variety of protecting groups may be used in the
manipulation of the above triazoles, amongst which is
the trityl group. This group may be easily attached by

30 reaction of the triazole with triphenylmethyl bromide or
chloride in an inert solvent such as methylene chloride
in the presence of an acid scavenger such as triethyl
amine. The trityl group may be later removed by
stirring or refluxing in an acidic medium such as

35 trifluoroacetic acid/water, HCl in methylene chloride,

or acetic acid/water. The trityl group may also be
hydrogenolyzed using a noble metal catalyst such as
palladium and hydrogen.

5   Scheme 26

E = CO_2R^{11}, CN, NO_2
P = protecting group
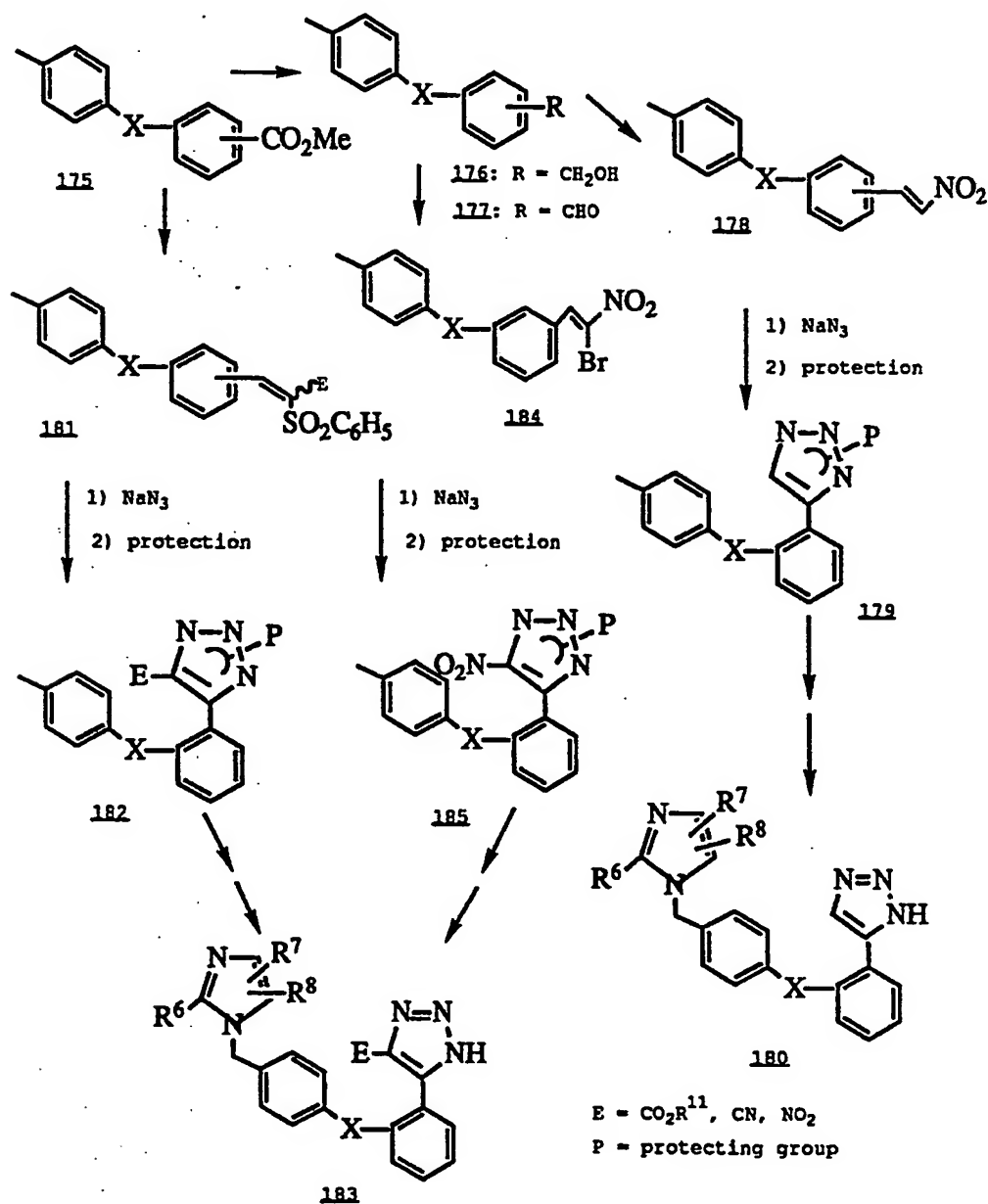
The synthesis of trifluoromethyl-1,2,4-triazoles
(190) is depicted in Scheme 27. Acid chloride (186) is
converted to amide (187) using standard procedures
familiar to one skilled in the art. A preferred
5   protecting group is the 2-propionitrile group
(P=CH$_2$CH$_2$CN). Thus (187; P=CH$_2$CH$_2$CN) can be synthesized
from (186) and ß-aminopropionitrile under Schotten-
Baumann like conditions, using aqueous base in an
organic solvent to help solubilize (186) and (187).
10 Amide (187) is converted to amidrazone (188) by reaction
with PCl$_5$ or phosgene to make an iminoyl chloride which
then in turn is reacted with excess hydrazine.
Amidrazone (188) is cyclized to the trifluoromethyl-
1,2,4-triazole (189) with trifluoroacetic anhydride and
15 then converted to 190 via bromination, alkylation and
deprotection as previously described.

Scheme 27

P = protecting group
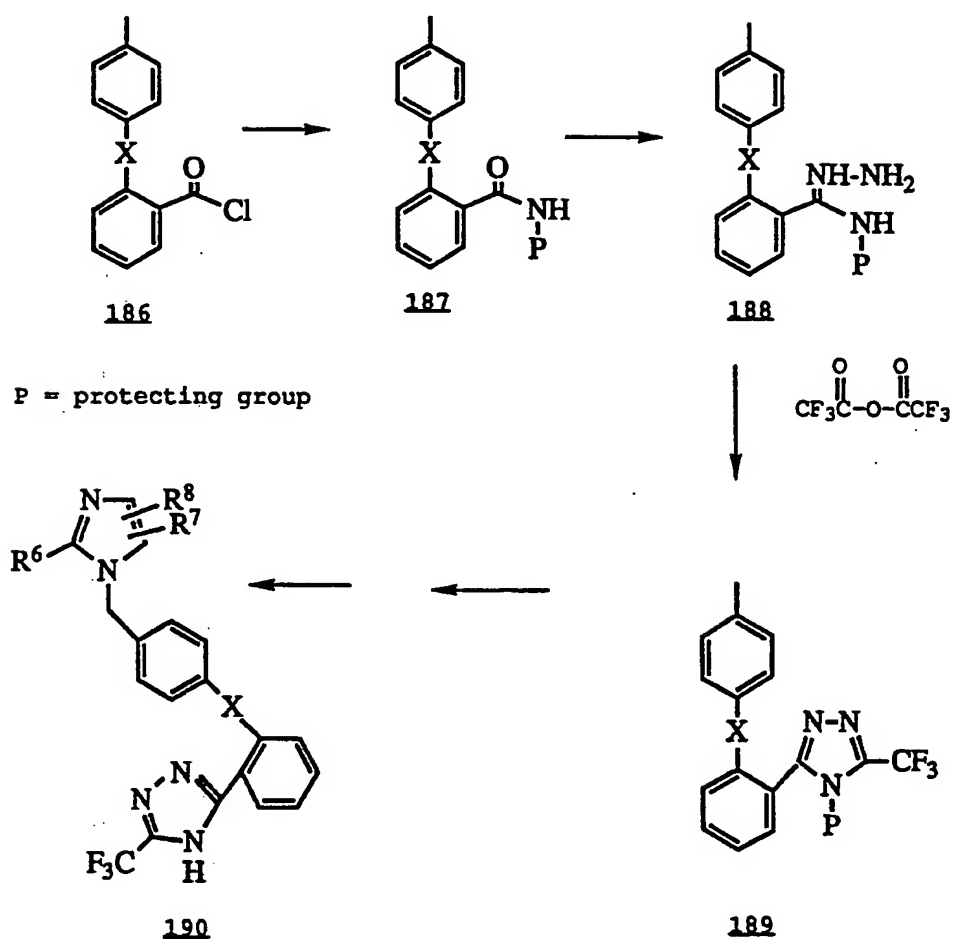
Pertinent R^6 groups may be variously introduced by
5   many procedures including those described in <u>Scheme 28</u>
which describes imidazole construction.

The R^6 groups so introduced may stand unchanged or
may be further elaborated if appropriately
functionalized, according to methods familiar to those
10   skilled in the art such as are illustrated in <u>Scheme 28</u>.

81

<u>Scheme 28</u>

R = CPh₃, SO₂Ph, CH₃CHOC₂H₅

192: R' = H   **193**: R' = Ts
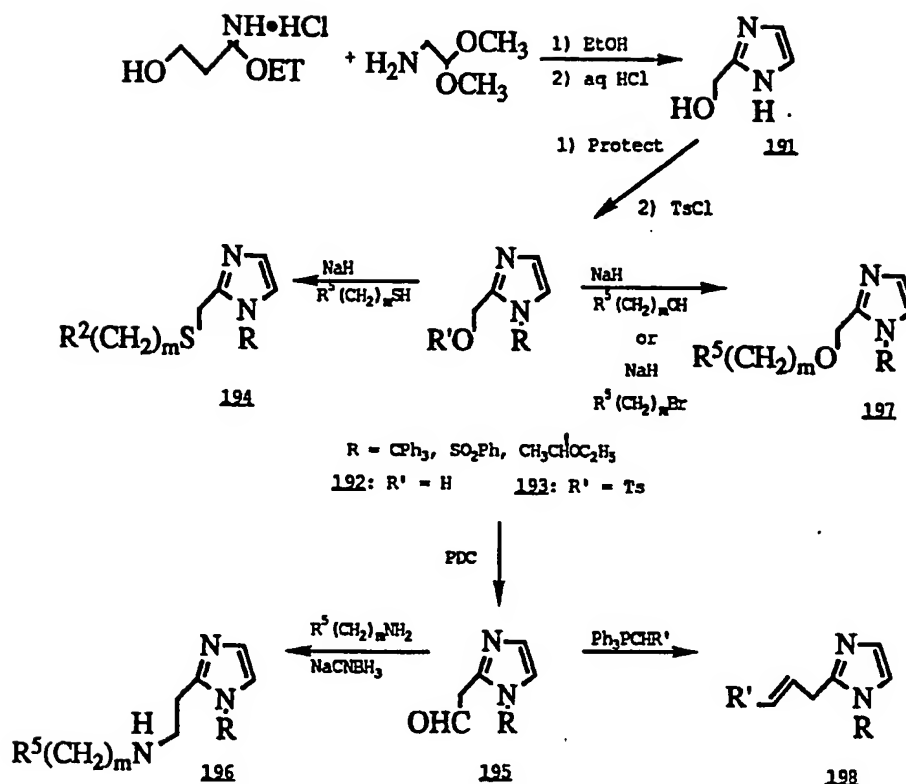
The 2-alkenylimidazoles (**201**) can be prepared by
bromination of the 2-alkylimidazoles (**199**) followed by
elimination of hydrogen bromide. The bromination is
preferably accomplished by UV-irradiation for 1-4 hours
of imidazole (**199**) and N-bromosuccinimide, in an inert
solvent, such as carbon tetrachloride at 25°C.
Treatment of the intermediate bromide (**200**) with a base,
such as DBU, triethylamine, or potassium t-butoxide,
affords the trans 2-alkenylimidazoles (**201**). Cis
alkenyl derivatives (**203**) are prepared from the trans
alkenyl compounds by treatment with osmium tetroxide and
sodium periodate to afford aldehydes (**202**) followed by
Wittig reaction.

82
Scheme 29

199   **200**   −HBr

201   **202**

$$R \!=\!\!\!=\!\! PPh_3$$

203
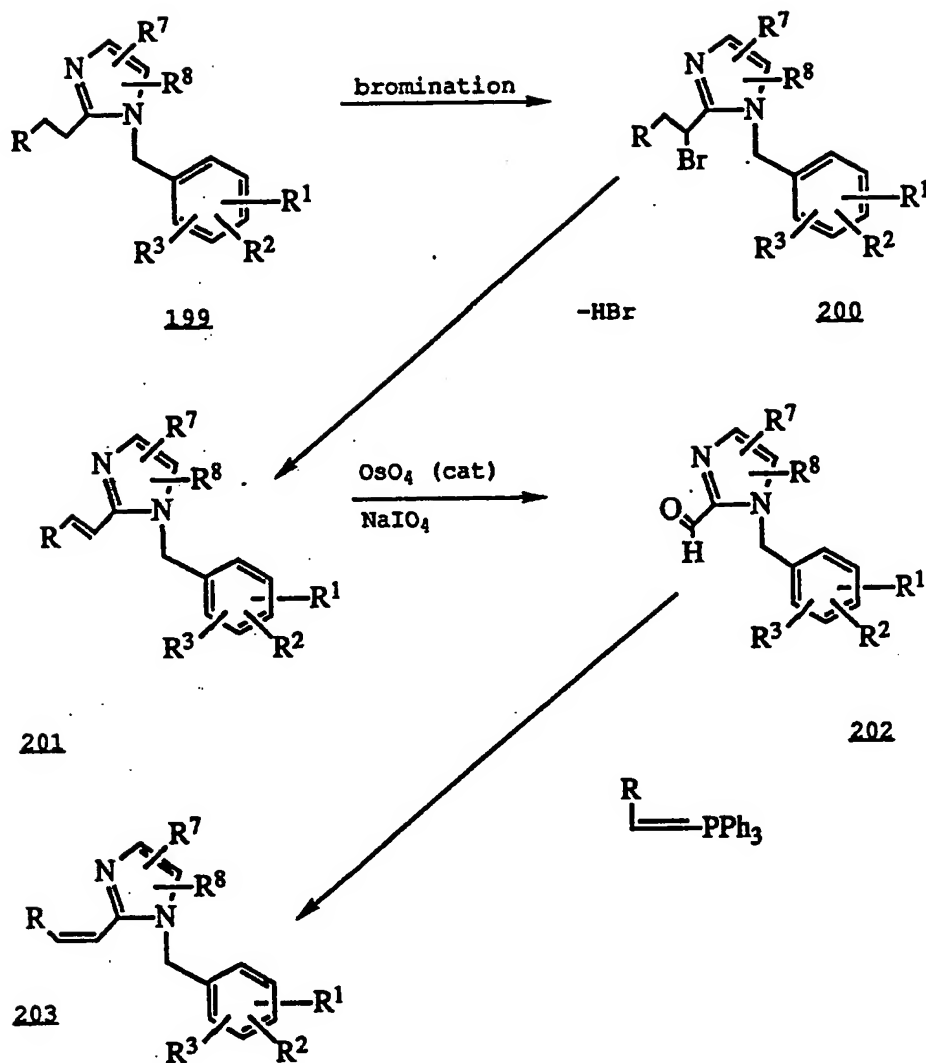
R = alkyl, cycloalkyl

Alternatively, R^6 groups may be introduced by
metallation of a protected imidazole or protected
5   2-methylimidazole followed by addition of an appropriate
electrophile as illustrated in Scheme 30, equations a)
and b). The products (alcohols, esters, halides,
aldehydes, alkyls) are suitable for further elaboration
by methods familiar to those skilled in the art.
10   Metallation of imidazoles is described in K.L. Kirk, J.

Org. Chem., 43, 4381 (1978); R.J. Sundberg, J. Het.
Chem., 14, 517 (1977); J.V. Hay et al., J. Org. Chem.,
38, 4379 (1973); B. Iddon, Heterocycles, 23, 417 (1985).

Condensation of 2-methylimidazole and appropriate
5   electrophiles (equation b) with catalytic acid or base
as described in A.R. Katritzky (Ed.), "Comprehensive
Heterocyclic Chemistry", Vol. 5, p. 431, Pergamon Press,
N.Y., 1984 affords products wherein R^6 is alkenyl which
are suitable for further elaboration.

10

Scheme 30

R = CPh₃, SO₂Ph
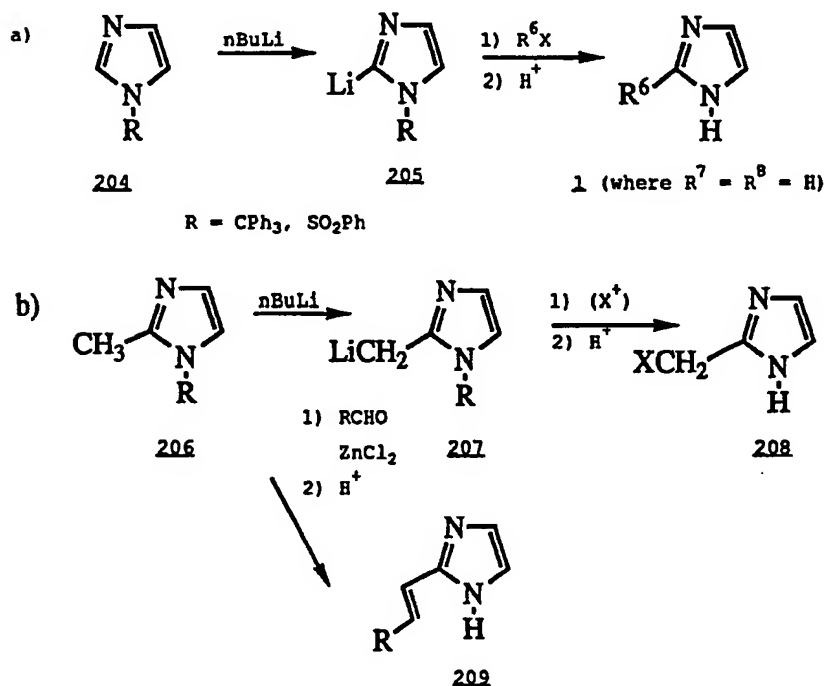
Various 2-substituted imidazoles can be prepared by
reaction of a protected 2-trimethylsilylimidazole with a
15   suitable electrophile by the method described by F.H.
Pinkerton and S.F. Thames, J. Het. Chem., 9, 67 (1972),
which can be further elaborated as desired.
Alternatively, R^6 may also be introduced by nickel
catalyzed cross-coupling of Grignard reagents with 2-
20   (methylthio)imidazoles (Scheme 31) as described by

E. Wenkert and T.W. Ferreira, <u>J. Chem. Soc., Chem. Commun.</u>, 840, (1982); E. Wenkert et al., <u>J. Chem. Soc., Chem. Commun.</u>, 637, (1979); and H. Sugimura and H. Takei, <u>Bull. Chem. Soc. Japan</u>, <u>58</u>, 664 (1985). The 2-

5   (methylthio)imidazoles can be produced by the procedure described in German Patent No. 2,618,370 and the references cited therein.

<u>Scheme 31</u>

10

$$
\text{KNCS} + \underset{\underset{\mathbb{R}^8}{|}}{\overset{\overset{H}{|}}{\text{RN-CHCH(OCH}_3)_2}} \xrightarrow{\text{EtOH}} \xrightarrow{\text{Aq HCl}} \quad \underset{\underset{\mathbb{R}}{\text{N}}}{\overset{\text{N}}{\text{HS}}} \underset{211}{\bigcirc} R^8 \xrightarrow{\text{CH}_3\text{I}}
$$

210

$$
\underset{\underset{\mathbb{R}}{\text{CH}_3\text{S}}}{\bigcirc} R^8 \quad \xrightarrow[\substack{\text{(Ph}_3\text{P)}_2\text{NiCl}_2 \\ \text{or} \\ \text{NiCl}_2\text{(dppp)}}]{\text{R}^6\text{MgCl}} \quad \underset{\underset{\mathbb{R}}{\text{R}^6}}{\bigcirc} R^8
$$

212   213
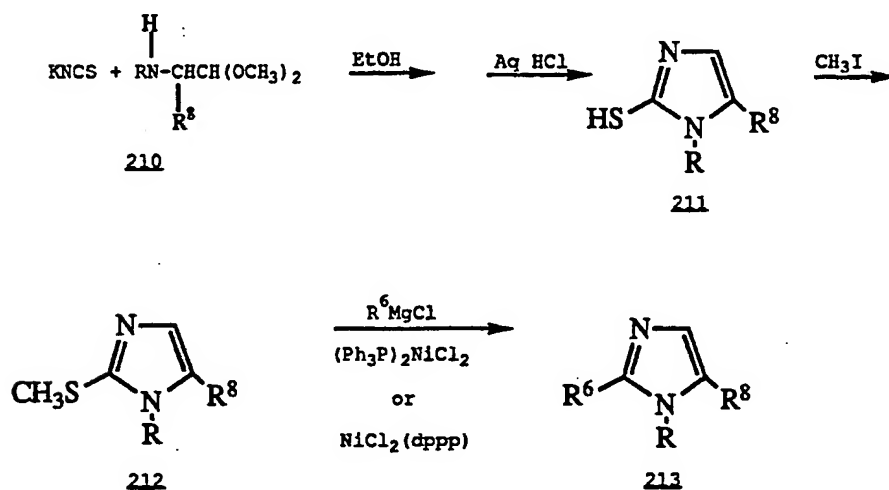
As shown in <u>Schemes 32-36</u>, elaboration of R^8 can be accomplished by some of the procedures described in

15   <u>Schemes 3</u> and <u>28</u>, by chain extension reactions familiar to those skilled in the art, or by degradation reactions such as conversion of an ester to an acid or an alkene to an aldehyde.

Specifically, the hydroxymethyl group can be

20   activated for the displacement reaction by reacting with thionyl chloride, PCl_5 or with carbon tetrachloride/ triphenylphosphine to form a corresponding chloro derivative. By a similar reaction bromo and iodo derivatives can be obtained. The hydroxymethyl group

25   can also be activated by forming the corresponding

85

p-toluenesulfonate, methanesulfonate and
trifluoromethane sulfonat derivatives.

Scheme 32

17

215   216

5
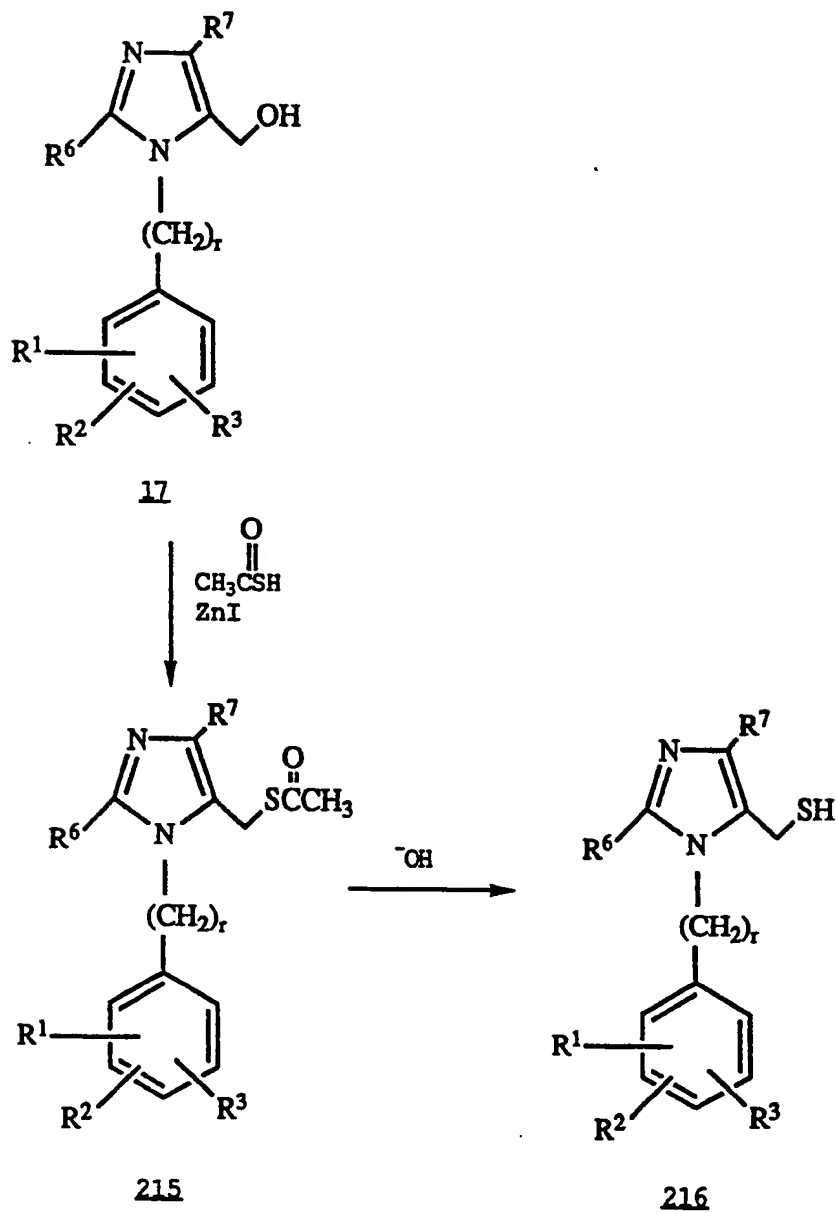
As shown in Scheme 32, the hydroxyl group can be
converted to thiolacetic acid derivative (215), J. Y.

Gauthier, *Tet. Lett.*, 15 (1986), and to thiol derivative
(216) by subsequent hydrolysis.

The hydroxymethyl group on compound (17) can be
readily oxidized to an aldehyde group by means of
5 manganese dioxide or ceric ammonium nitrate. The
aldehyde group will undergo chain extension reactions
such as the Wittig and Wittig-Horner reactions and enter
into typical carbon-carbon bond forming reactions with
Grignard and lithium reagents as well as with compounds
10 bearing activated methylene groups. Alternatively, the
hydroxymethyl group can be oxidized directly to an acid
functionality which can in turn be converted to ester
and amide derivatives. The esters and amides can be
prepared directly from the aldehydes by manganese
15 dioxide oxidation in the presence of sodium cyanide and
an alcohol or amine, *J. Am. Chem. Sec.*, 90, 5616 (1968)
and *J. Chem. Soc.* (C), 2355 (1971).

As shown in *Scheme 33*, the chlorine on compound
(25) can be displaced by the anion of dialkyl malonate
20 to give the corresponding malonate derivative (217).
The saponification of (217) with NaOH (or KOH) gives the
corresponding diacid which can be decarboxylated to give
the corresponding propionic acid derivative (218) by
heating to 120°C. Alternatively, (218) can be directly
25 obtained by refluxing (217) with a mineral acid such as
HCl or sulfuric acid. The free acid (218) can be
esterified by heating in a medium of the various
alcohols and a catalytic amount of mineral acids such as
HCl or sulfuric acid to give the corresponding esters
30 (219). Alternatively the esters can be obtained by
reacting the free acid (218) and the corresponding
alcohols in the presence of coupling reagents such as
DDQ or EEDQ. A similar reaction with various mono-
substituted and disubstituted amines produces the
35 corresponding amides (220). A similar reaction with

various mercaptans produces the corresponding
thioesters.

Scheme 33
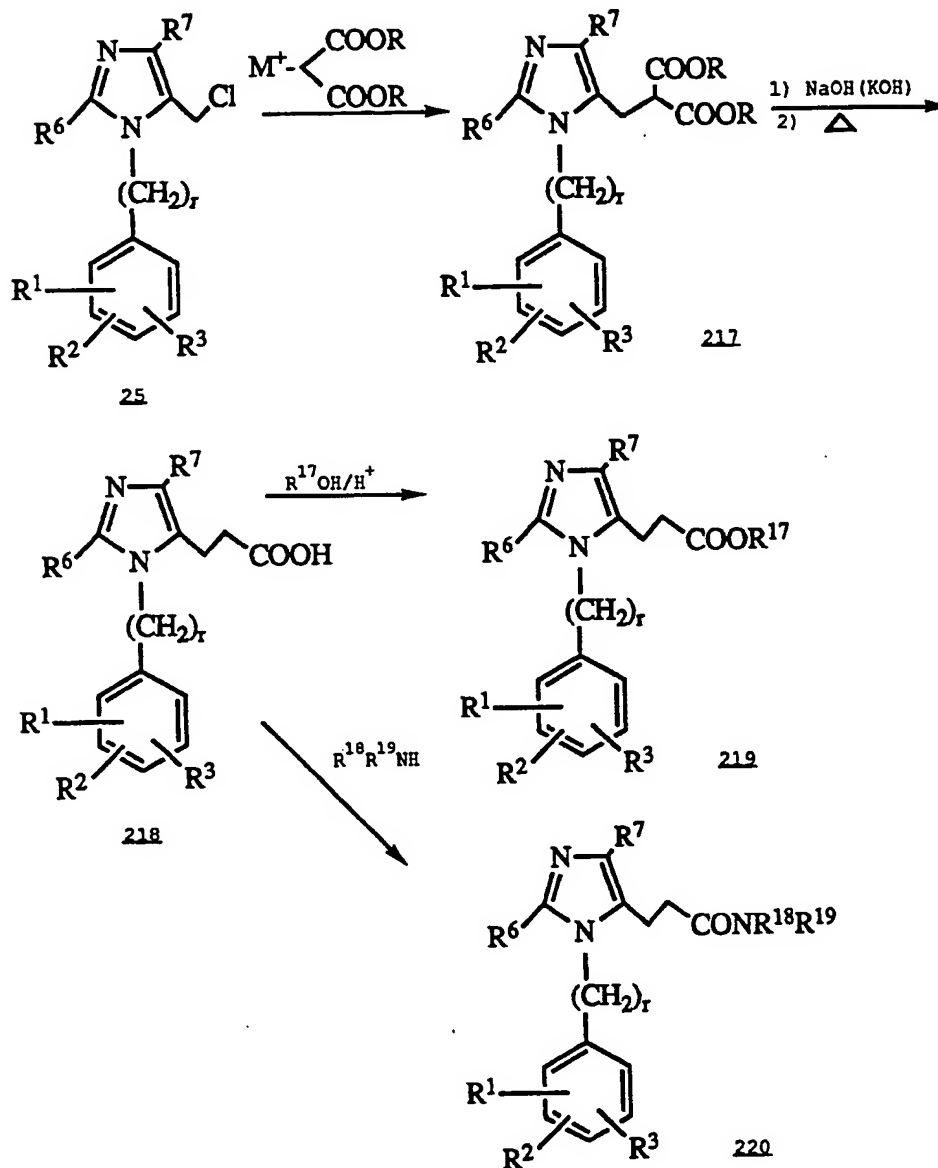
As shown in Scheme 34, the chloro group on (25) can
be displaced by the sodium salt or potassium salt of the
alkyl, aryl or arylalkyl mercaptans to give the

88

corresponding sulfide derivatives (221). The amine
derivative (222) can be obtained by treating (25) with
ammonia or with the corresponding mono-substituted
amines. Alternatively, the chloro group may be

5 displaced by sodium azide to give an azide intermediate
which upon reduction with H_2 over a noble metal catalyst
or with a reducing agent such as chromous chloride
(W. K. Warburton, J. Chem. Soc., 2651 (1961)) yields
(222) where R^{10} and R^{11} are hydrogen. This amine can

10 be subsequently alkylated with alkyl halides, or
reductively alkylated with aldehydes and ketones to give
alkyl derivatives of (222). The amines (222) are
converted to the corresponding carbamates (224),
sulfonamides (225), amides (226) or ureas (227) by

15 standard procedures illustrated in Scheme 34 and
familiar to one skilled in the art.

Scheme 34
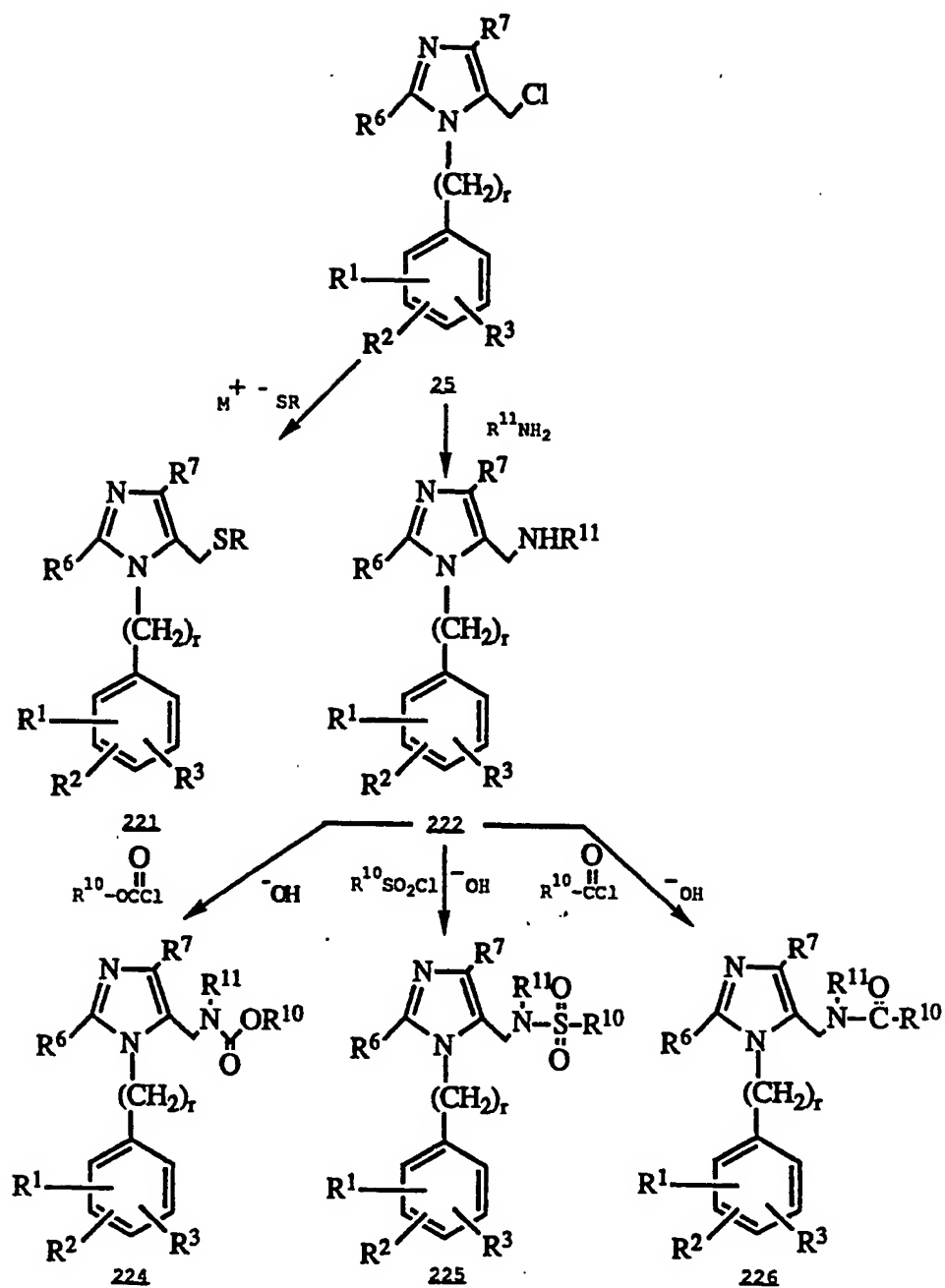
Scheme 34 (continued)

227
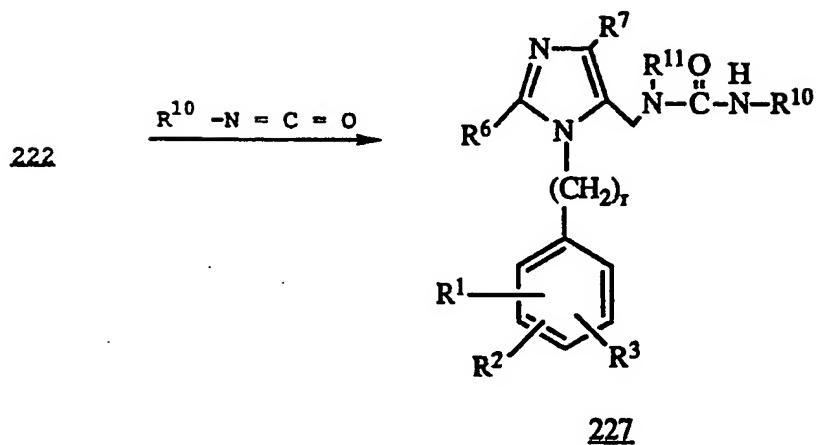
The reaction between the thiopyridyl ester (229) and a suitable Grignard reagent produces the ketones 5   (230).

Scheme 35

229   (R = pyridyl)   230

(where R[16] = alkyl, cycloalkyl, $(CH_2)_pC_6H_5$)

10
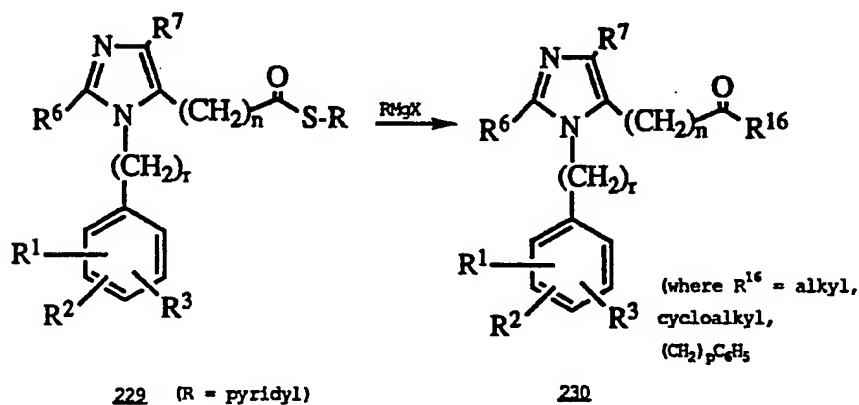
As shown in Scheme 36 when the imidazole 4- and/or 5-position contains an aldehyde (231) then reaction with organometallic reagents such as Grignard or alkyl/aryllithium reagents will yield alcohols (232) 15   which in turn may be transformed into a variety of other functionality familiar to one skilled in the art.
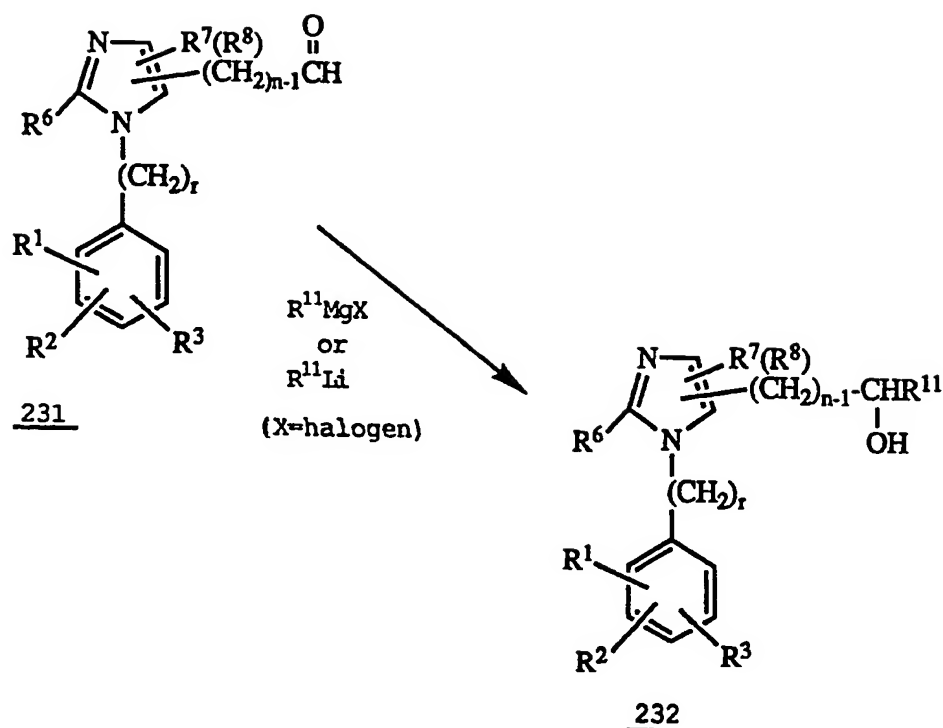
Scheme 36

As shown in Scheme 37, ester 234 may be obtained by direct oxidation of aldehyde 233 with NaCN, MnO$_2$ in methanol (Corey, E. J., et al. J. Am. Chem. Soc. (1968) 90, 5616). Oxidation of 233 with NaCN, MnO$_2$, and an amine in 2-propanol leads to the corresponding amide 235 (Gilman, N. W. Chem. Comm. (1971) 733).

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Scheme 37

233

234

R = alkyl

235   R' or R" = H or alkyl

236
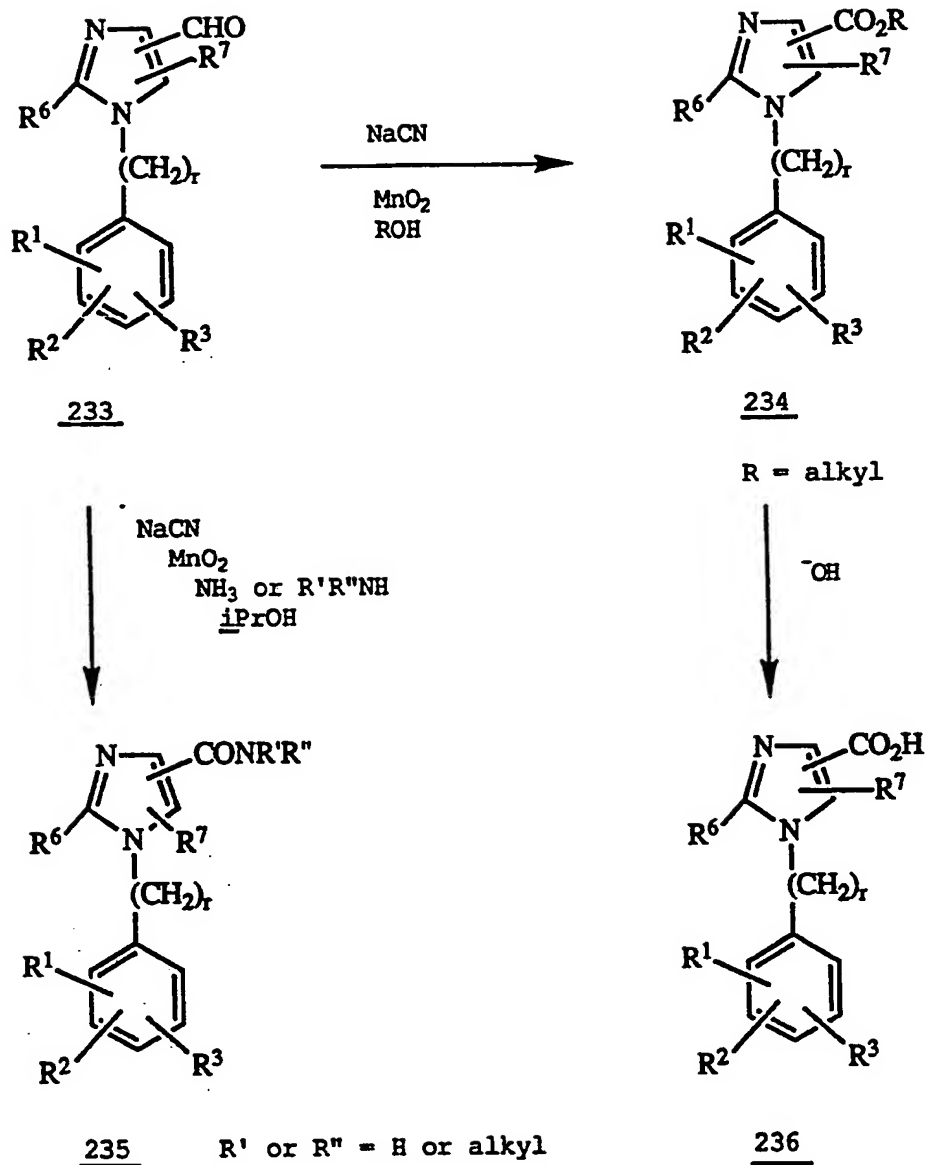
5   Saponification of ester 234 will lead to carboxylic
acid 236.
         Aldehyde 233, in turn, may be made from the
corresponding alcohol 17 by a variety of methods
familiar to one skilled in the art, including pyridium

chlorochromate (PCC), Swern and ceric ammonium nitrate (CAN) oxidations.

Likewise, the unalkylated hydroxymethylimidazole derivative $1(R^8=CH_2OH)$ may undergo the transformations

5   to the aldehyde, ester, carboxylic acid and carboxamide by the reactions mentioned above for the alkylated case.

Compounds 238 (where Ar = aryl or heteroaryl as described in the scope under the definition of R^7) can be prepared by the coupling of an arylmetal derivative

10 (ArM, where M = ZnBr, Me_3Sn, $B(OH)_2$, etc.) with a haloimidazole 237 in the presence of a transition metal catalyst such as palladium, nickel, platinum, zirconium, etc. (Scheme 38a). Alternatively an imidazole metal derivative 239 can be coupled to an arylhalide to

15 prepare 238 (Scheme 38b).

The arylmethyl derivatives 240 can be prepared employing the transition metal catalysed coupling of 237 and an arylmethylmetal ($ArCH_2M'$, where M' = ZnBr, etc.), as shown in Scheme 38c.

20 Compounds 241 may be prepared, as described in Scheme 38d by the coupling of an alkenyl or alkynylmetal drivative (AM) or the corresponding alkene or alkyne (AH) with 237.

Likewise, the unalkylated imidazoles (1, where R^7 =

25 Br or I) may undergo the coupling reactions described in Scheme 38a-d [For references to transition metal catalysed coupling reactions, see Richard C. Heck, Palladium Reagents in Organic Synthesis, Academic Press, New York, Chapters 6, 7 and 8; and references cited

30 therein].

The compounds of formula I where R^7 is an arylalkenyl group or an arylalkynyl group and the carbon-carbon double or triple bond is not adjacent to the imidazole ring (e.g., $R^7 = (CH_2)_uCH=CH(CH_2)_vAr$,

35 where u ≠ 0) can be prepared by a variety of chain

elongation methods and chain coupling reactions known to one skilled in the art including thos described in Schemes 3, 28, 29, 33, 35, 36, and 38.

The compounds of formula I where R^7 is an arylalkyl
5   group ($R^7 = (CH_2)_w Ar$, where $w = 2-10$) can be prepared by reduction of the corresponding alkenes (241) by catalytic hydrogenation.

Scheme 38

a)

237

(X = Br or I)

238

Ar = aryl or heteroaryl

b)

239

238

c)   237

240

Scheme 38 (continued)

d)   237

$$\xrightarrow[\text{Pd}^0]{\text{AM or AH}}$$

A = C≡C(CH$_2$)$_x$A$_r$

or

CH=CH(CH$_2$)$_x$Ar

X = 0-8
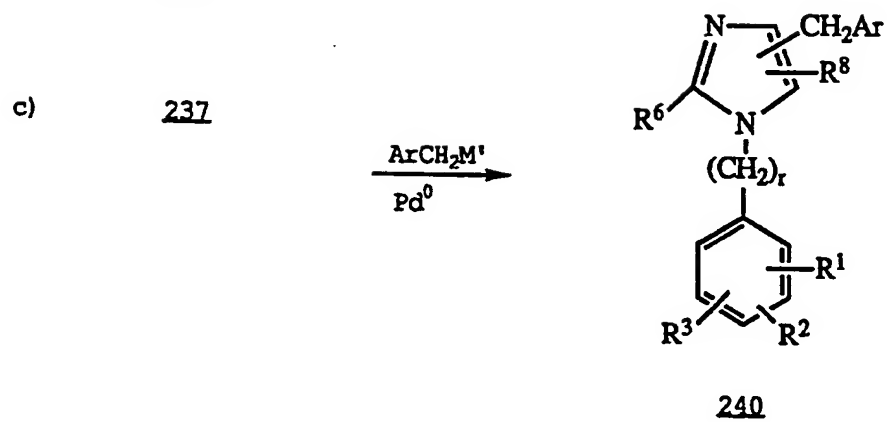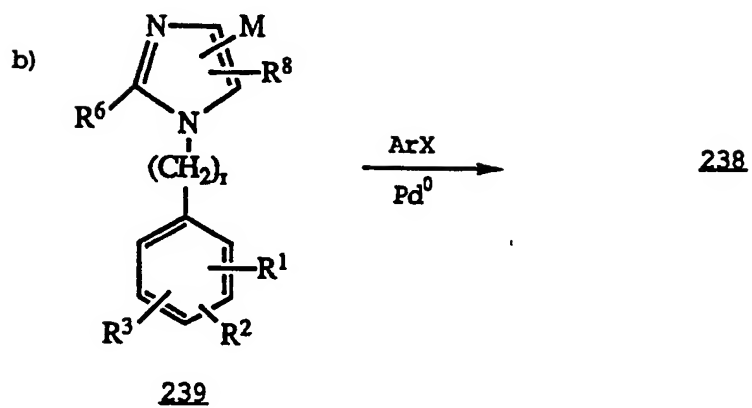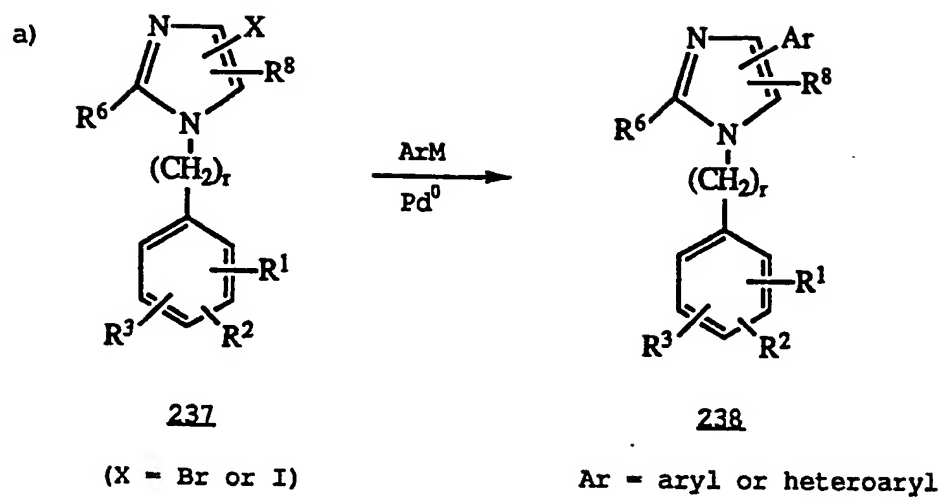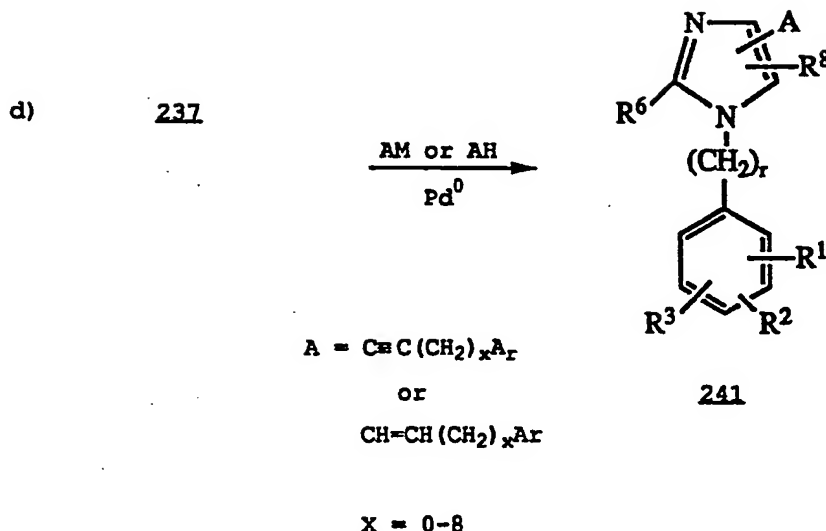
Compounds of formula I where R^7 = arylalkenyl and R^8 = CH$_2$OH, aldehyde, or COOH can be prepared as shown

5   in Scheme 39.

2-Alkylimidazole-4,5-dicarboxylic acids (242), prepared by the method of R.G. Fargher and F.L. Pyman (J. Chem. Soc., 1919, 115, 217), can be converted into their corresponding diesters (243) by simply refluxing

10   in an alcohol solvent in the presence of an acid such as HCl, or by many other methods familiar to one skilled in the art.

Diester (243) can then be converted into its metallic salt by reaction with sodium methoxide, sodium

15   ethoxide, sodium hydride, potassium hydride or any other base in an appropriate solvent such as DMF. The resultant salt is then alkylated with the appropriately substituted benzyl derivative (2) to yield benzylimidazole (244). The above alkylation sequence

20   may be also performed by heating or refluxing the benzyl halide (tosylate or mesylate) (2) with imidazole (243) in a solvent such as DMF in the presence of an acid scavenger such as potassium or sodium carbonate.

Diester (244) can be reduced with lithium aluminum
hydride in an inert solvent such as THF to the
corresponding dialcohol (245). Selective oxidation of
dialcohol (245) with manganese dioxide in an inert
5   solvent such as THF yields primarily aldehyde (247) with
a minor product dialdehyde (246). Separation of (247)
from (246) either by crystallization or
chromatographically, followed by Wittig reaction of
(247) with the appropriately substituted
10 arylalkylidenetriphenylphosphorane in an inert solvent
such as THF yields the 4-arylalkenyl-5- hydroxymethyl-
imidazole (248). Further oxidation of (248) with the
Dess-Martin periodinane (J. Org. Chem., 1983, 48, 4155),
with manganese dioxide, with pyridinium chlorochromate,
15 with barium manganate or with other oxidants familiar to
one skilled in the art, in an inert solvent such as THF
or methylene chloride followed by deprotection of either
R^1, R^2, or R^3 if necessary yields the 4-arylalkenyl-
imidazole-5-carboxaldehyde (249).
20   Oxidation of (249) with, for example, manganese
dioxide/cyanide ion (Corey, E.J., et al. J. Am. Chem.
Soc., 1968, 90, 5616) or with potassium permanganate
(Sam, D.J. et al. J. Am. Chem. Soc., 1972, 94, 4024)
yields 4-arylalkenylimidazole-5-carboxylic acid (250).

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Scheme 39
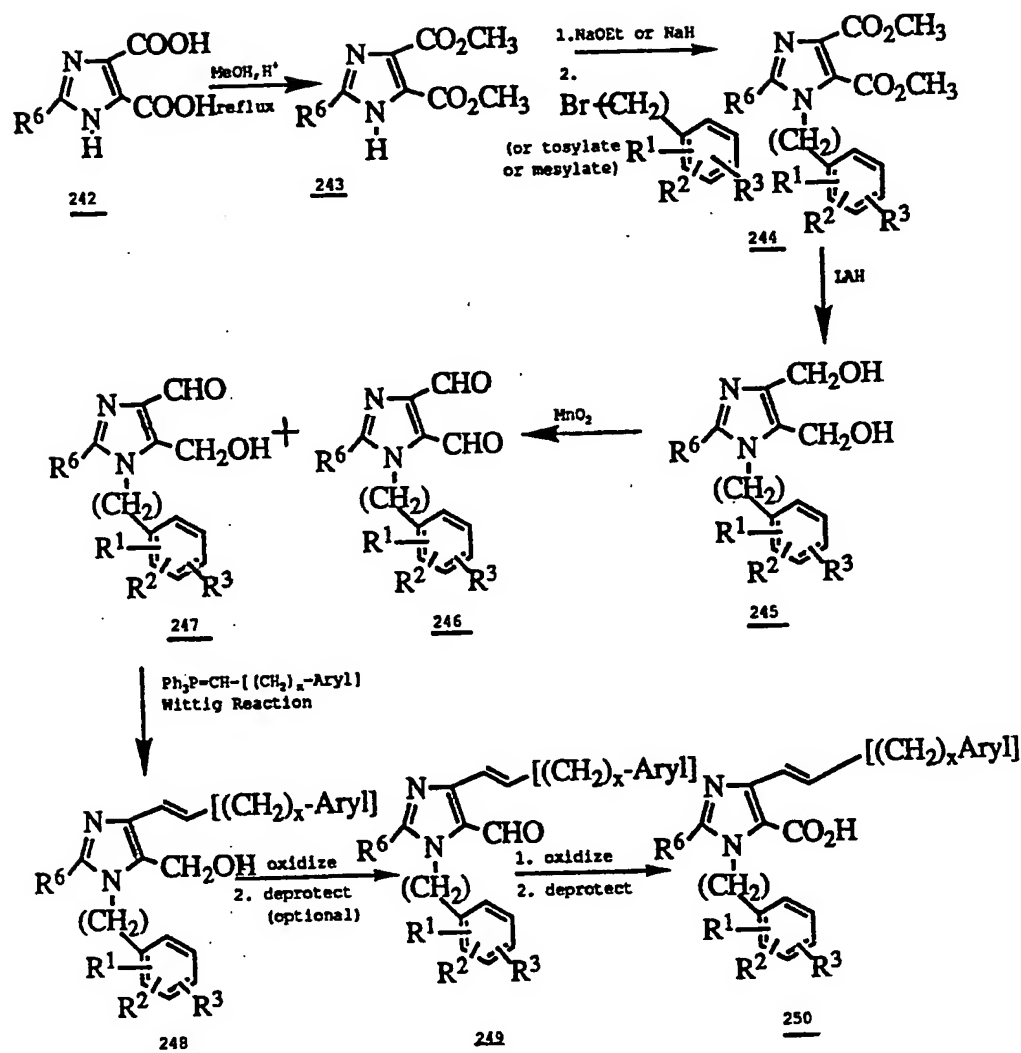
5   Imidazoles represented by structure (251) where X

is Cl, Br or I and E is an electron withdrawing group

such as an ester, ketone, nitro, alkylsulfonyl,

arylsulfonyl, etc., can undergo the nucleophilic

aromatic substitution reaction (H. Schubert, H. Simon,

10   A. Jumar Z. Chem. (1968) 62-63) where the leaving group

X is substituted by a nucleophile such as sulfur,

carbon, or nitrogen to yield adducts (252) (Scheme 40).

The reaction can be done in a hydroxylic solvent such as

99

methanol or non-hydroxylic solvent such as DMSO at room
temperature to the reflux temperature of the solvent.
The nucleophile sometimes must be converted into its
anion to make it more nucleophilic. For example,
5   thionaphthol can be refluxed in methanol in the presence
of sodium methoxide and the haloimidazole (251). Other
nucleophiles include other arylthiols, heteroarylthiols,
arylsulfonamides, heteroarylsulfonamides, arylamines,
heteroarylamines, etc., familiar to one skilled in the
10 art.

If a sulfur nucleophile is used, the resultant
sulfides can be oxidized to the corresponding sulfoxides
and sulfones by methods familiar to one skilled in the
art.

15

Scheme 40

251   252
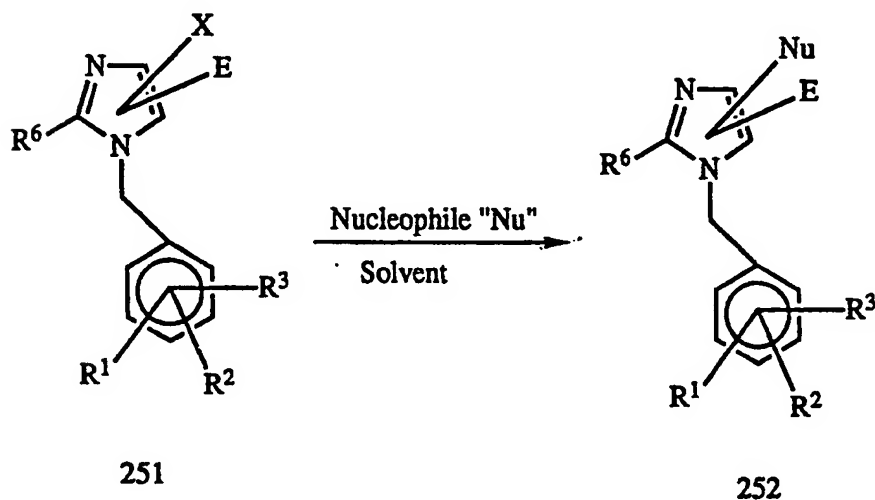
20   The compounds of this invention and their
preparation can be understood further by the following
examples, which do not constitute a limitation of the
invention. In these examples, unless otherwise
indicated, all temperatures are in degrees centigrade
25 and parts and percentages are by weight.

100

Example 1

CH2OH structure
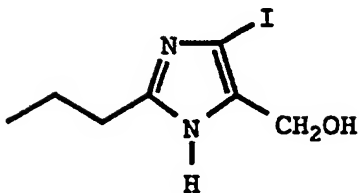
5   PART A: Preparation of 5-hydroxymethyl-4-iodo-2-n-
                propylimidazole.

_____

A solution of 31.5 g of 4(5)-hydroxymethyl-2-n-
10 propylimidazole and 50.6 g of N-iodosuccinimide in 560
mL of 1,4-dioxane and 480 mL of 2-methoxyethanol was
stirred at 45°C for 2 h. The solvents then were removed
under vacuum. The resulting solids were washed with
distilled water and then were dried to afford 54.6 g of
15 the product as a yellow solid: mp 169-170°C. NMR
(DMSO-d_6) δ 12.06 (br s, 1H); 5.08 (t, 1H); 4.27 (d, 2H);
2.50 (t, 2H); 1.59 (sext., 2H); 0.84 (t, 3H).

CHO structure
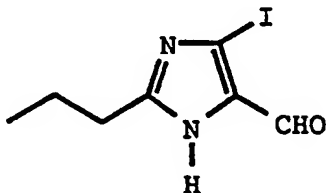
20

Part B: Preparation of 4-iodo-2-n-propylimidazole-5-
           carboxaldehyde

_____

25   To a solution of 35.8 g of 5-hydroxymethyl-4-iodo-
2-n-propylimidazole in 325 mL of glacial acetic acid at
20°C was added dropwise over 1 h 290 mL of 1.0 N aqueous
ceric ammonium nitrate solution. The resulting mixture
was stirred at 20°C for 1 h. The reaction mixture then

101

was diluted with water, adjusted to pH 5-6 employing
aqueous sodium hydroxide solution, and extracted with
chloroform. The combined organic phases were washed
with water and brine, dried over anhydrous sodium

5   sulfate, filtered, and concentrated. The resulting
crude solid was recrystallized from 1-chlorobutane to
furnish 29.9 g of product as a light yellow solid; mp
141-142°C. NMR (CDCl$_3$) δ 11.51 (br s, 1H); 9.43 (s,
1H); 2.81 (t, 2H); 1.81 (sext. 2H); 0.97 (t, 3H).

10
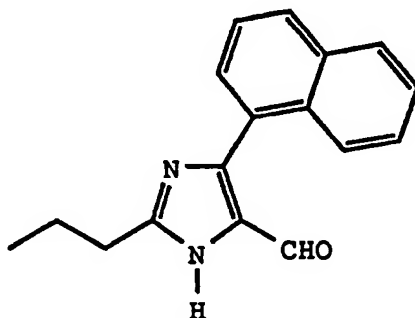
PART C: Preparation of 4-(naphth-1-yl)-2-n-
           propylimidazole-5-carboxaldehyde.

15   _____

     A solution of 2.64 g (0.01 mol) of 4-iodo-2-
n-propylimidazole-5-carboxaldehyde, toluene (40 mL), and
0.33 g (0.00029 mol) of tetrakistriphenylphosphine

20   palladium (0) was stirred at room temperature under
nitrogen, while a solution of 3.44 g (0.022 mol) of
1-naphthylboronic acid in 50 mL of ethanol was slowly
added. The reaction was stirred for 5 minutes, after
which 12 mL of 2M sodium carbonate was slowly added.

25   After the addition was completed, the reaction was
refluxed for 48 h and cooled. The reaction was
filtered, the filtrate was evaporated under reduced
pressure, and the resulting residue was dissolved in 300
mL of methylene chloride, washed twice with 100 mL of

saturated sodium chloride solution, washed twice with
100 mL of distilled water, and washed twice with 300 mL
of 10% HCl. The HCl layer was made basic with 50%
sodium hydroxide until the pH=10. At this point, the
5 basic water layer was extracted three times with 300 mL
of methylene chloride, the methylene chloride layer was
dried over sodium sulfate and evaporated under reduced
pressure. Yield: 0.90 g (0.0034 mol, 34%) of product.
NMR (CDCl$_3$) δ 11.45 (m, 1H); 9.42 (s, 1H); 7.28 (m, 7H);
10 2.82 (t, 2H); 1.85 (m, 2H); 1.01 (t, 3H).
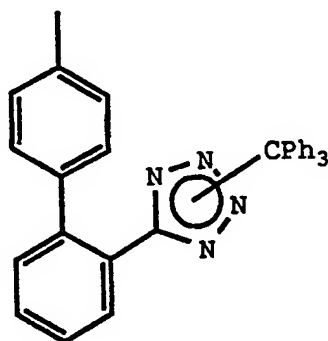
Part D: Preparation of 4-Methyl-2'-(N-triphenyl-
15   methyl-(1H-tetrazol-5-yl))biphenyl

    4'-Methylbiphenyl-2-nitrile (preparation described
in European patent application 0253310, published on
20 20.01.88) (10.00 g, 51.7 mmol, 1 eq), tri-n-butyltin
chloride (14.0 mL, 51.7 mmol, 1 eq), sodium azide (3.4 g
51.7 mmol, 1 eq), and xylene (50 mL) were mixed and
refluxed for 64 h after which the reaction mixture was
cooled to room temperature. 10.0 N NaOH (6.10 mL, .061
25 mmol, 1.2 eq) and trityl chloride (14.99 g, 53.8 mmol,
1.04 eq) were then added and the mixture stirred for 24
h after which water (39 mL) and heptane (100 mL) were
added. The resultant slurry was stirred at 0°C for 1.5
h. The resultant solids thus obtained were filtered,

washed with water (2X55 mL) washed once with 3:2
heptane/toluene (55 mL) and dried overnight under high
vacuum to yield 19.97 g of a light yellow powder; mp
148.0-155.0°C (dec.). These solids were slurried in
5   ethyl acetate (75 mL) and filtered to yield 15.0 g of a
light yellow powder: mp 164.0-165.5°C (dec.). NMR
(CDCl$_3$) δ 7.91 (d, 1H, J=9Hz); 7.53-7.18 (m, 13H); 7.02-
6.84 (m, 9H); 2.25 (s, 3H).
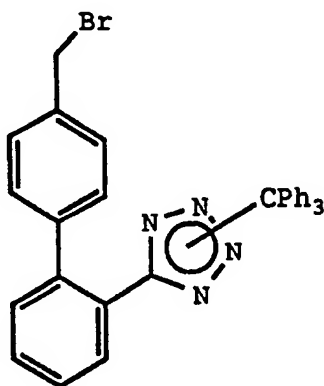
10

Part E: Preparation of 4-Bromomethyl-2'-(N-triphenyl-
           methyl-(1H-tetrazol-5-yl))biphenyl,
           a representative procedure.

15   _____

        4-Methyl-2'-(N-triphenylmethyl-(1H-tetrazol-5-
yl))biphenyl (52.07 g, 109 mmol, 1 eq; for preparation,
see Example 95, Part B), N-bromosuccinimide (19.4 g, 109
20   mmol, 1 eq), benzoyl peroxide (1.0 g) and carbon
tetrachloride (300 mL) were mixed and refluxed for 2. 5
h. The reaction was cooled to room temperature and the
succinimide filtered. The filtrate was concentrated and
the residue triturated with ether to yield a first crop
25   of 36.0 g:mp 129.5-133.0°C (dec.). NMR (CDCl$_3$) δ 4.37
(CH$_2$Br). This material was suitable for further
transformation.

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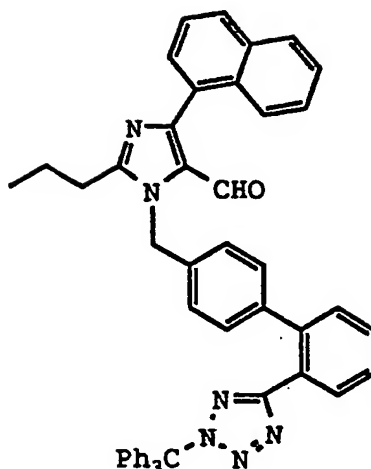
Part F: Preparation of 4-(naphth-1-yl)-2-n-propyl-1-
           [(2'-(N-triphenylmethyl-(1H-tetrazol-5-yl))
           biphenyl-4-yl)methyl]imidazole-5-carboxal-
           dehyde.

        A suspension of 4-(naphth-1-yl)-2-n-propyl-
imidazole-5-carboxaldehyde (0.90 g, 39.7 mmol, 1 eq),
4-bromomethyl-2'-(N-triphenylmethyl-(1H-tetrazol-5-
yl))biphenyl (2.03 g, 43.7 mmol), 1.1 eq), dry DMF (20
mL), and 3.0 g of potassium carbonate was stirred at
room temperature for 18 h. The reaction mixture was
filtered, the precipitate was washed with methylene
chloride and evaporated under reduced pressure. The
residue was chromatographed in 98:2 methylene
chloride/ethyl acetate over silica gel to yield a yellow
foam. Yield: 1.50 g. NMR (CDCl$_3$) δ 9.45 (s, 1H); 7.85
(m, 1H); 6.86-7.45 (m, 29H); 5.55 (s, 2H); 2.60 (t, 2H);
1.80 (m, 2H); 0.95 (t, 3H).

105
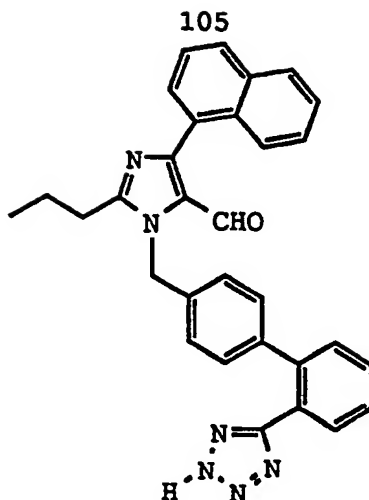
Part G: Preparation of 4-(naphth-1-yl)-2-n-propyl-1-
[(2'-(1H-tetrazol-5-yl)biphenyl-4-
yl)methyl]imidazole-5-carboxaldehyde.

4-(Naphth-1-yl)-2-n-propyl-1-[(2'-(N-triphenyl-
methyl-(1H-tetrazol-5-yl))biphenyl-4-yl)methyl]-
imidazole-5-carboxaldehyde (1.50 g), THF (80 mL), and
10% HCl were stirred at room temperature. After 8 hr,
the mixture was poured into ice/5% NaOH and the pH was
adjusted to 10. The resultant solids were filtered and
the pH of the filtrate was adjusted to 4-5 with 10% HCl.
The turbide solution was extracted with 80/20 methylene
chloride/i-propanol (3X100 mL), the organic phase was
dried over sodium sulfate and evaporated under reduced
pressure to yield 0.51 g of a white glass. NMR (CDCl$_3$)
δ 9.35 (s, 1H); 7.78 (m, 1H); 7.60-7.38 (m, 2H);
7.35-6.96 (m, 12H); 5.62 (s, 1H); 2.60 (m, 2H); 1.85 (m,
2H); 0.90 (t, 3H).

The following intermediates can be prepared by the
method described in Example 1, Part C.

106

Table 1

5	R^6	R^7	mp (°C)
	n-propyl		
	n-propyl		
10	n-propyl		
	n-propyl		
	n-propyl		
15			

107

Table 1 (continued)

| R⁶ | R⁷ | mp (°C) |

5

R^6	R^7	mp (°C)
n-propyl		wax[a]
n-propyl		wax[b]
n-propyl		wax[c]
n-propyl		wax[d]
n-propyl		wax[e]
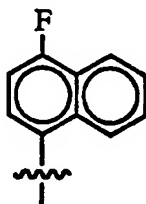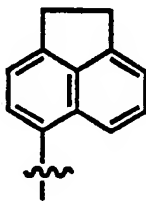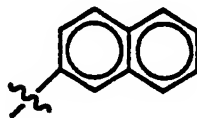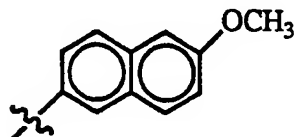
Table 1 (continued)

5	R^6	R^7	mp (°C)

| n-propyl | | |
| n-propyl | | |

10
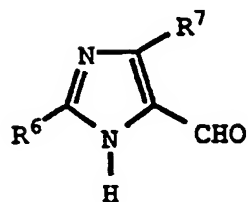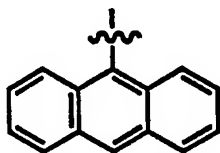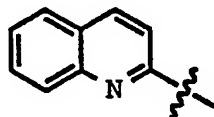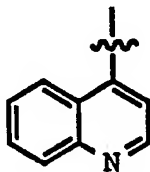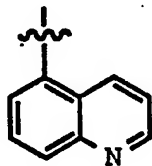
n-propyl		
n-propyl		
n-propyl		
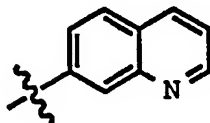
15

| n-propyl | | |
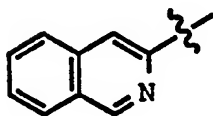
[a]NMR (DMSO-D$_6$) ∂ 10.04 (s, 1H), 8.135 (s, 1H), 7.20-7.99
     (m, 4H), 2.65 (t, 2H), 1.71 (m, 2H), 0.94 (t, 3H).

[b]NMR (CDCl$_3$) ∂ 9.44 (s, 1H), 8.55 (m, 2H), 8.15 (m, 2H),
     7.20 (m, 2H), 2.85 (t, 2H), 1.73 (m, 2H), 1.03 (t,
     3H).

[c]NMR (CDCl$_3$) ∂ 9.53 (s, 1H), 7.74 (m, 1H), 7.64 (m, 1H),
     7.28 (m, 2H), 3.73 (q, 2H), 3.40 (s, 4H), 1.87 (m,
     2H), 1.24 (t, 3H)

[d]NMR (CDCl$_3$) ∂ 9.88 (s, 1H), 8.22 (s, 1H), 7.88 (m, 4H),
     7.53 (m, 2H), 2.87 (t, 2H), 1.87 (m, 2H), 1.03 (t,
     3H).

[e]NMR (DMSO-D$_6$) ∂ 9.85 (s, 1H), 8.30 (s, 1H), 8.14 (s,
     1H), 7.60-7.90 (m, 2H), 7.01-7.21 (m, 2H), 3.93 (s,
     3H), 2.78 (t, 2H), 1.85 (m, 2H), 1.01 (t, 3H).

     The compounds in Table 2 can be made by the
procedure described in Example 1 or by methods described
in European Patent Application 0253310 (publication
date: 20.01.88).

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Table 2
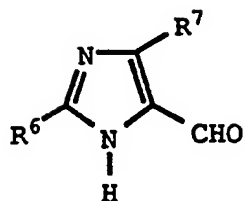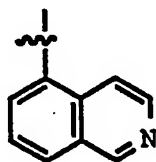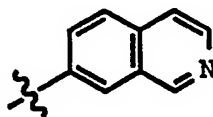
	R[6]	R[7]	mp (°C)

n-propyl
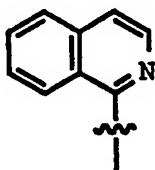
n-propyl
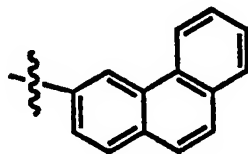
n-propyl
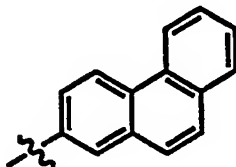
n-propyl

n-propyl
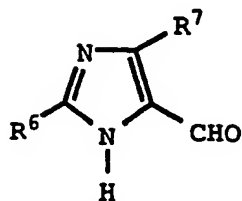
Table 2 (continued)
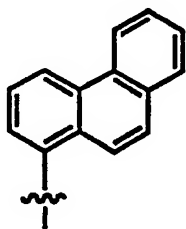
R[6]	R[7]	mp(°C)
n-propyl		
n-propyl		wax[a]
n-propyl		
n-propyl		
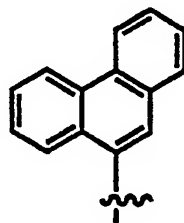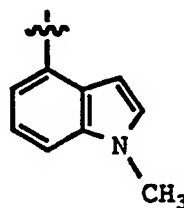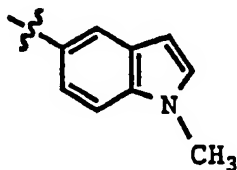
[a]NMR (CDCl$_3$) δ 9.54 (s, 1H), 8.74 (m, 2H), 8.20 (b, 1H), 7.85 (s, 1H), 7.60-774 (m, 4H), 2.90 (t, 2H), 1.92 (m, 2H), 1.08 (t, 3H).
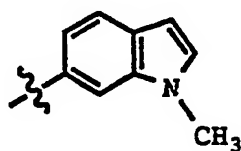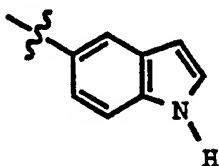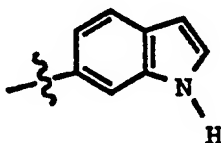
Table 2 (continued)

5

R^6	R^7	mp (°C)
n-propyl		
n-propyl		
n-propyl		
n-propyl		
n-propyl		

10

15

Table 2 (continued)

5	R⁶	R⁷	mp (°C)

Table 2 (continued)

R^6	R^7	mp (°C)
n-propyl		
n-propyl		
n-propyl		
n-propyl		
n-propyl		

Table 2 (continued)

5	R^6	R^7	mp (°C)
	n-propyl		
	n-propyl		
10	n-propyl		
	n-propyl		wax^a

15

^{a}NMR (CDCl$_3$) δ 10.13 (s, 1H), 7.66 (m, 2H), 7.43 (s,
1H),7.29 (m, 2H), 2.65 (t, 2H), 1.74 (m, 2H), 0.92 (t,
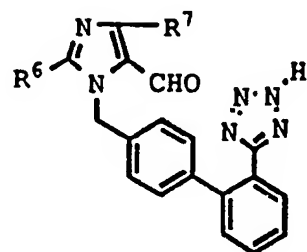20 3H).

Examples 2-94 in Tables 3 and 4 can be prepared by
the methods described in Example 1 and by methods
described in European Patent Application 0253310
(publication date: 20.01.88).

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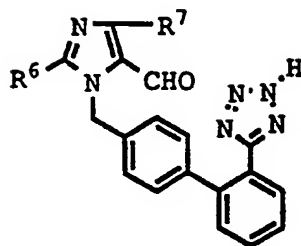
Table 3

5	Ex. No.	R^6	R^7	mp (°C)
	2	n-propyl		
	3	n-propyl		
10	4	n-propyl		
	5	n-propyl		

Table 3 (continued)

Ex. No.	R^6	R^7	mp (°C)
6	n-propyl		
7	n-propyl		glass[a]
8	n-propyl		glass[b]
9	n-propyl		130 dec
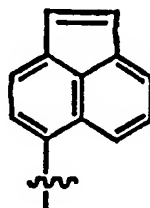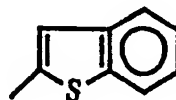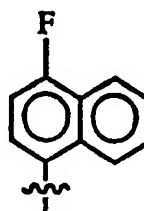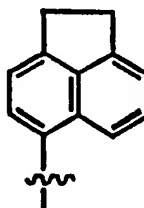
Table 3 (continued)
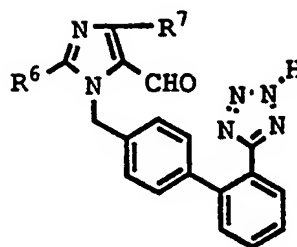
Ex. No.	R⁶	R⁷	mp (°C)
10	n-propyl		glass[c]
11	n-propyl		wax[d]
12	n-propyl		
13	n-propyl		
14	n-propyl		
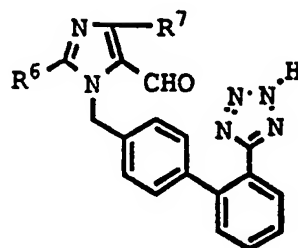
Table 3 (continued)

5	Ex. No.	R⁶	R⁷	mp (°C)

	15	n-propyl		
	16	n-propyl		
10	17	n-propyl		
	18	n-propyl		
	19	n-propyl		
15				
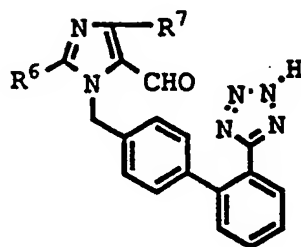
Table 3 (continued)

Ex. No.	R⁶	R⁷	mp (°C)
20	n-propyl		
21	n-propyl		
22	n-propyl		
23	n-propyl		

Table 3 (continued)
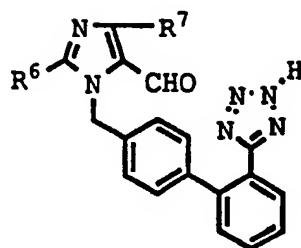
Ex. No.	R6	R7	mp (°C)
24	n-propyl		glass^e
25	n-propyl		
26	n-propyl		
27	n-propyl		

Table 3 (continued)
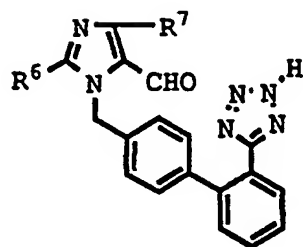
5	Ex. No.	R^6	R^7	mp (°C)
	28	n-propyl		
	29	n-propyl		
10	30	n-propyl		
	31	n-propyl		
	32	n-propyl		
15				

Table 3 (continued)

	Ex. No.	R⁶	R⁷	mp (°C)

5
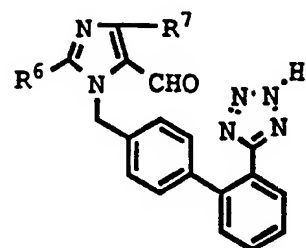
33   n-propyl

34

n-propyl

10

36

n-propyl

37   n-propyl

38

n-propyl

15

Table 3 (continued)
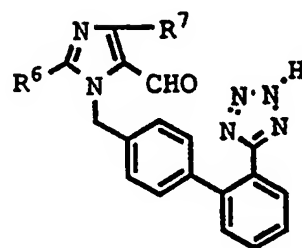
	Ex. No.	R^6	R^7	mp (°C)
5				
	39	n-propyl		
	40	n-propyl		
10				
	41	n-propyl		glass^f

[a]NMR (CDC13) ∂ 10.03 (s, 1H), 7.94 (m, 1H), 7.84 (m, 1H), 7.77 (s, 1H), 7.54 (m, 1H), 7.38 (m, 4H), 7.24 (m, 1H), 7.18 (d, 2H), 7.05 (d, 2H), 5.58 (d, 2H), 2.61 (t, 2H), 1.78 (m, 2H), 0.95 (t, 3H).

5 [b]NMR (CDC13) ∂ 9.37 (s, 1H), 8.10 (m, 1H), 7.92 (m, 1H), 6.92-7.62 (m, 10H), 5.66 (s, 2H), 2.65 (t, 2H), 1.80 (m, 2H), 1.04 (t, 3H).

[c]NMR (CDC13) ∂ 9.77 (s, 1H), 8.05 (m, 1H), 7.85 (m, 2H), 7.00-7.83 (m, 10H), 6.95 (m, 1H), 5.61 (s, 2H),

10   2.59 (t, 2H),1.81 (m, 2H), 1.01 (t, 3H).

[d]NMR (CDC13) ∂ 9.76 (s, 1H), 8.14 (m, 1H), 7.92 (m, 2H), 7.73 (m, 2H), 7.55 (m, 3H), 7.28 (m, 4H), 7.11 (m, 2H), 5.64 (s, 2H), 3.96 (s, 3H), 2.63 (t, 2H), 1.76 (m, 2H), 1.01 (t, 3H).

15 [e]NMR (CDC13) ∂ 9.46 (s, 1H), 8.67 (m, 1H), 7.88 (m, 1H), 7.41-7.65 (m, 6H), 6.90-7.34 (m, 10H), 5.30 (s, 2H), 2.62 (t, 2H), 1.78 (m, 2H), 1.06 (t, 3H)

[f]NMR (CDC13) ∂ 10.45 (s, 1H), 8.00 (m, 1H), 7.46-7.62 (m, 4H), 7.23-7.40 (m, 5H), 7.23 (d, 2H), 7.02 (d,

20   2H), 5.56 (s, 2H), 2.58 (t, 2H), 1.74 (m, 2H), 0.94 (t, 3H)
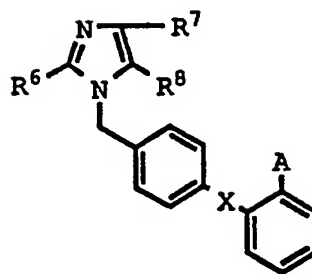
Table 4

5	Ex. No.	R6	R7	R8	X	A	mp (°C)

| 42 | | n-propyl | | COOH | single bond | CN4H | |

10
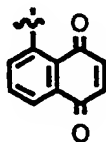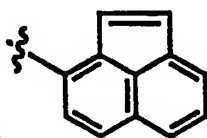
| 43 | | n-propyl | | COOH | single bond | CN4H | |

| 15 | 44 | n-propyl | | COOH | single bond | CN4H | |
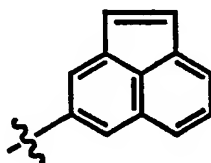
Table 4 (continued)
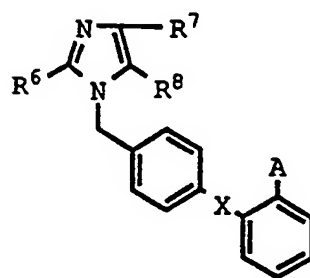
5	Ex. No.	R^6	R^7	R^8	X	A	mp (°C)
	45	n-propyl	(acenaphthylene)		COOH	single bond	CN_4H
10	46	n-propyl	(acenaphthene)		COOH	single bond	CN_4H
	47	n-propyl	(acenaphthene)		CHO	single bond	COOH

Table 4 (continued)
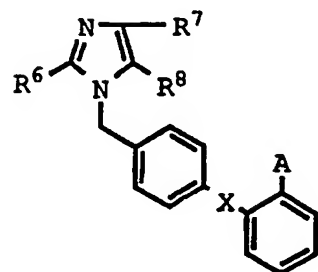
5 Ex. No.	R⁶	R⁷	R⁸	X	A	mp (°C)
48	n-propyl		CHO	single bond	COOH	
49	n-propyl		CHO	single bond	COOH	
50	n-propyl		CHO	single bond	COOH	
51	n-propyl		CHO	single bond	COOH	

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Table 4 (continued)

$$R^6 - \text{imidazole} - R^7, R^8 - CH_2 - C_6H_4 - X - \overset{A}{\underset{}{C_6H_4}}$$
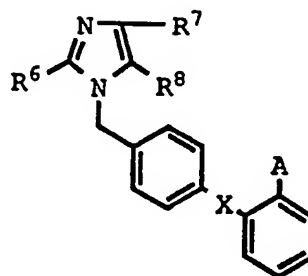
Ex. No.	R^6	R^7	R^8	X	A	mp (°C)
52	n-propyl	quinolin-2-yl	CHO	single bond	COOH	
53	n-propyl	quinolin-4-yl	CHO	single bond	NHSO$_2$CF$_3$	
54	n-propyl	quinolin-5-yl	CHO	single bond	NHSO$_2$CF$_3$	

Table 4 (continued)
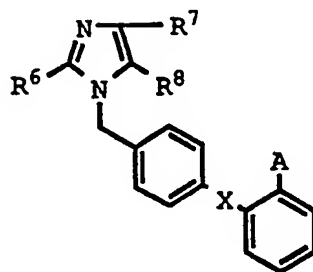
	Ex. No.	R^6	R^7	R^8	X	A	mp (^{O}C)
5							
	55	n-propyl		CHO	single bond	NHSO$_2$CF$_3$	
10							
	56	n-propyl		CHO	single bond	NHSO$_2$CF$_3$	
	57	n-propyl		CHO	single bond	NHSO$_2$CF$_3$	
15							
	58	n-propyl		CHO	single bond	NHSO$_2$CF$_3$	
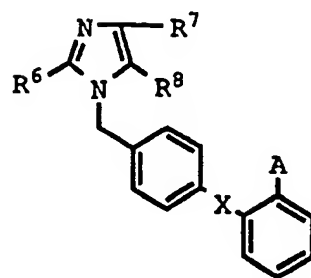
Table 4 (continued)

Ex. No.	R⁶	R⁷	R⁸	X	A	mp (°C)

| 59 | n-propyl | | CHO | -NHCO- | CN₄H | |

| 60 | n-propyl | | CHO | -O- | CN₄H | |

| 61 | n-propyl | | CHO | -S- | CN₄H | |

Table 4 (continued)
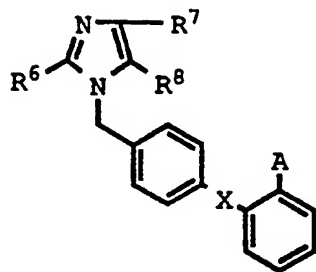
Ex. No.	R⁶	R⁷	R⁸	X	A	mp (°C)
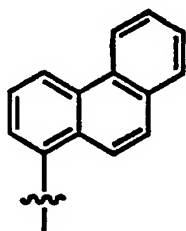
| 62 | n-propyl | | CHO | -CO- | CN_4H | |

| 63 | n-propyl | | CHO | $-OCH_2-$ | CN_4H | |

| 64 | n-propyl | | CHO | -CH=CH- | CN_4H | |
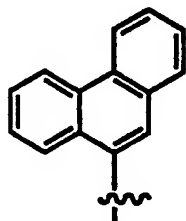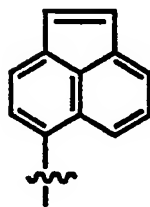
Table 4 (continued)
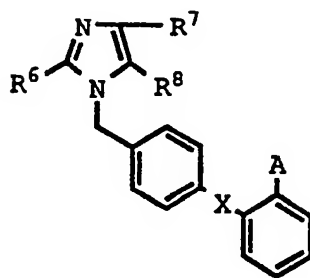
	Ex. No.	R⁶	R⁷	R⁸	X	A	mp (°C)

Ex. No.	R⁶	R⁷	R⁸	X	A
65	n-propyl		CH_2OH	single bond	CN_4H
66	n-propyl		CH_2OH	single bond	CN_4H
67	n-propyl		CH_2OH	single bond	CN_4H
68	n-propyl		CH_2OH	single bond	CN_4H

Table 4 (continued)
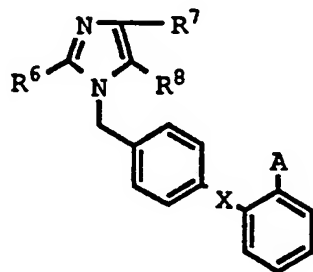
	Ex. No.	R^6	R^7	R^8	X	A	mp (^{O}C)
	69	n-propyl		CH$_2$OH	single bond	CN$_4$H	
	70	n-propyl		CH$_2$OH	single bond	CN$_4$H	
	71	n-propyl		CH$_2$OH	single bond	CN$_4$H	
	72	n-propyl		CH$_2$OH	single bond	CN$_4$H	

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Table 4 (continued)
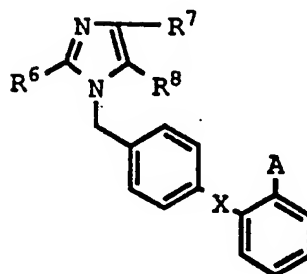
Ex. No.	R^6	R^7	R^8	X	A	mp (°C)
73	n-propyl		CH_2OH	single bond	CN_4H	
74	n-propyl		CH_2OH	single bond	CN_4H	
75	n-propyl		CH_2OH	single bond	CN_4H	
76	n-propyl		CH_2OH	single bond	CN_4H	

Tabl 4 (continued)
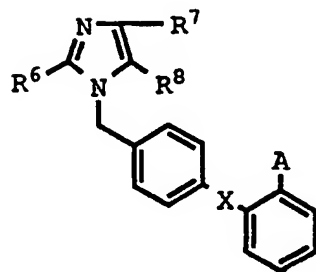
Ex. No.	R⁶	R⁷	R⁸	X	A	mp (°C)
77	n-propyl		CH_2OH	single bond	CN_4H	
78	n-propyl		CH_2OH	single bond	CN_4H	
79	n-propyl		CH_2OH	single bond	CN_4H	
80	n-propyl		CHO	single bond	CN_4H	
81	n-propyl	$-CH=CH-$	CHO	single bond	CN_4H	

Table 4 (continu d)
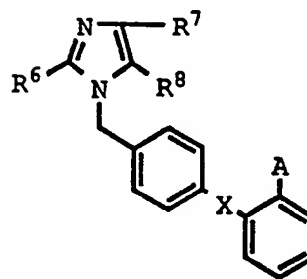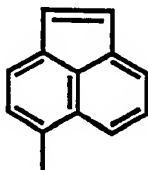
Ex. No.	R^6	R^7	R^8	X	A	mp ($^\circ$C)
82	n-propyl	$-CH_2$	CHO	single bond	CN_4H	
83	n-propyl	$-CH_2 \cdot C \equiv C$	COOH	$-NH-CO-$	CN_4H	
84	n-propyl	$-CH_2-CH=CH$	COOH	$-O-$	COOH	
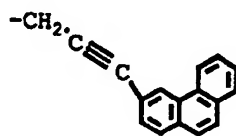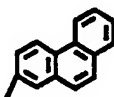
138

Tabl 4 (continued)

Ex. No.	R^6	R^7	R^8	X	A	mp ($^\circ$C)
85	n-propyl	(C≡CCH$_2$–)	CHO	–OCH$_2$–	–NHSO$_2$CF$_3$	
86	n-propyl	(C≡C CH$_2$–)	CHO	–CH=CH–	–NHSO$_2$CF$_3$	
87	n-propyl	(–CH$_2$–)	COOH	–CO–	–NHSO$_2$CF$_3$	
88	n-propyl	–CH$_2$CH$_2$	COOH	–O–	–NHSO$_2$CF$_3$	

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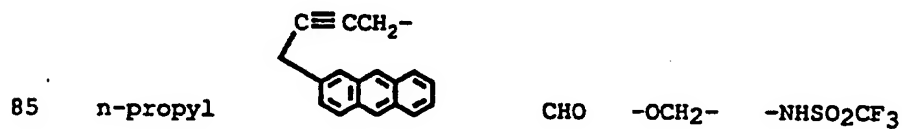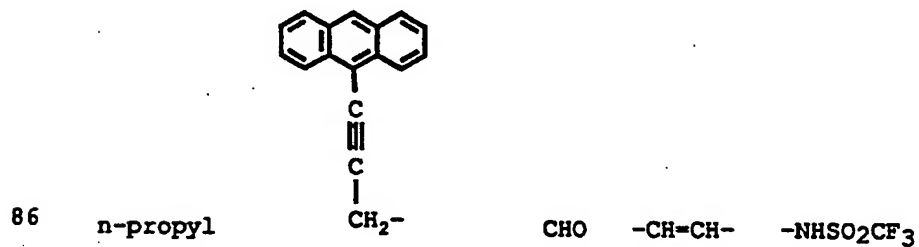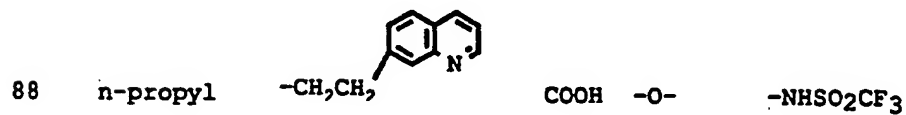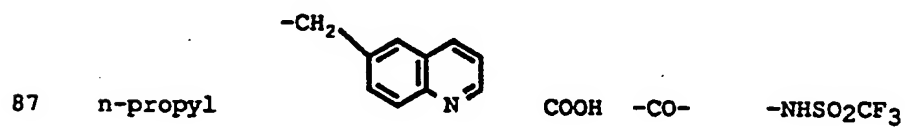
Table 4 (continued)
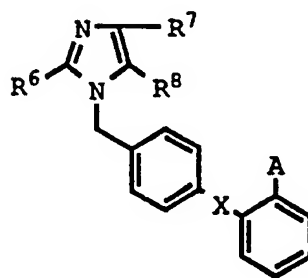
Ex. No.	R^6	R^7	R^8	X	A	mp (°C)
89	n-propyl	CH=CH–	CH$_2$OH	–S–	CN$_4$H	
90	n-butyl	–CH$_2$–	CHO	–CO–	COOH	
91	n-butyl	CH=CH–	CHO	–OCH$_2$–	COOH	
92	n-butyl		CHO	–CH=CH–	COOH	

Table 4 (continued)
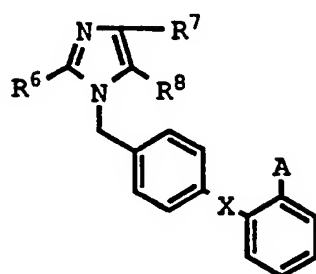
5	Ex. No.	R^6	R^7	R^8	X	A	mp ($^\circ$C)

	93	n-butyl		COOH	-CO-	COOH	

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	94	n-butyl		COOH	-NHCO-	COOH	

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Example 95
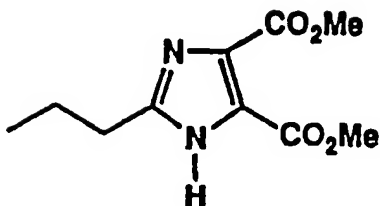
PART A: Preparation of 2-n-Propyl-4,5-dicarbomethoxy-
           imidazole

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2-n-Propylimidazole-4,5-dicarboxylic acid [prepared
by the method of R. G. Fargher and F. L. Pyman (J. Chem.
Soc., 1919, 115, 217), mp 257 (dec.) °C] (17.14 g, 86.6
mmol, 1 eq), methanol (400 mL) and acetyl chloride (38.1
mL), 534 mmol, 6 eq) were cautiously mixed (acetyl
chloride addition to methanol is very exothermic) and
refluxed overnight. The solvent was removed in vacuo
and water (100 mL) and 10 N NaOH were added until pH=7.
The aqueous mixture was extracted with ethyl acetate
(3X), the organic layers combined, dried (MgSO$_4$) and the
solvent removed in vacuo to yield 12.00 g of a white
solid. Recrystallization from hexane/ethyl acetate
yielded 11.41 g of a white solid (58%); mp:
162.0-164.5°C. NMR (CDCl$_3$) δ 3.95 (s, 6H); 2.78 (t,
2H); 1.83 (t of t, 2H, J=7,7 Hz); 0.97 (t, 3H, J=7 Hz);
IR (neat) 1735 cm^{-1}. Anal. calcd. for
C$_{10}$H$_{14}$N$_2$O$_4$•(H$_2$O)$_{0.25}$: C, 52.06; H, 6.28; N, 12.14.
Found: C, 52.06; H, 6.17; N, 12.49.

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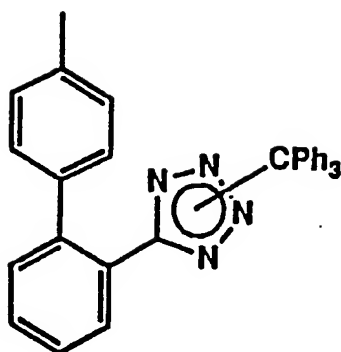
10   PART B: Preparation of 4-Methyl-2'-(N-triphenylmethyl-
                 (1H-tetrazol-5-yl))biphenyl

      4'-Methylbiphenyl-2-nitrile (preparation described
15   in European Patent Application 0253310, published on
      20.01.88) (10.00 g, 51.7 mmol, 1 eq), tri-n-butyltin
      chloride (14.0 mL, 51.7 mmol, 1 eq), sodium azide (3.4
      g, 51.7 mmol, 1 eq), and xylene (50 mL) were mixed and
      refluxed for 64 h after which the reaction mixture was
20   cooled to room temperature. 10.0 N NaOH (6.10 mL, .061
      mmol), 1.2 eq) and trityl chloride (14.99 g, 53.8 mmol,
      1.04 eq) were then added and the mixture stirred for 24
      h after which water (30 mL) and heptane (100 mL) were
      added. The resultant slurry was stirred at 0°C for 1.5
25   h. The resultant solids thus obtained were filtered,
      washed with water (2 x 55 mL) washed once with 3:2
      heptane/toluene (55 mL) and dried overnight under high
      vacuum to yield 19.97 g of a light yellow powder: mp
      148.0-155.0°C (dec.). These solids were slurried in
30   ethyl acetate (75 mL) and filtered to yield 15.0 g of a
      light yellow powder: mp 164.0-165.5°C (dec.). NMR
      (CDCl$_3$) δ 7.91 (d, 1H, J=9 Hz); 7.53-7.18 (m, 13H);
      7.02-6.84 (m, 9H); 2.25 (s, 3H).
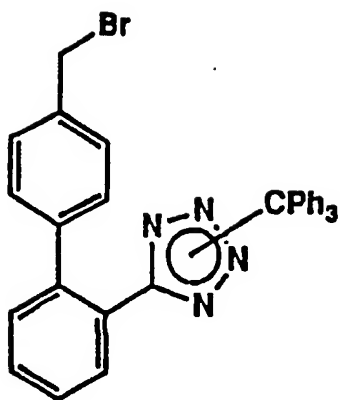
PART C: Preparation of 4-Bromomethyl-2'-(N-triphenyl-
           methyl-(1H-tetrazol-5-yl))biphenyl-4-yl)methyl
           bromide, a representative procedure

           4-Methyl-2'-(N-triphenylmethyl-(1H-tetrazol-5-
yl))biphenyl (52.07 g, 109 mmol, 1 eq), N-
bromosuccinimide (19.4 g, 109 mmol, 1 eq), benzoyl
peroxide (1.0 g) and carbon tetrachloride (300 mL) were
mixed and refluxed for 2.5 h. The reaction was cooled
to room temperature and the succinimide filtered. The
filtrate was concentrated and the residue triturated
with ether to yield a first crop of 36.0 g: mp 129.5-
133.0°C (dec.). NMR (CDCl$_3$) δ 4.37 (CH$_2$Br). This
material was suitable for further transformation.
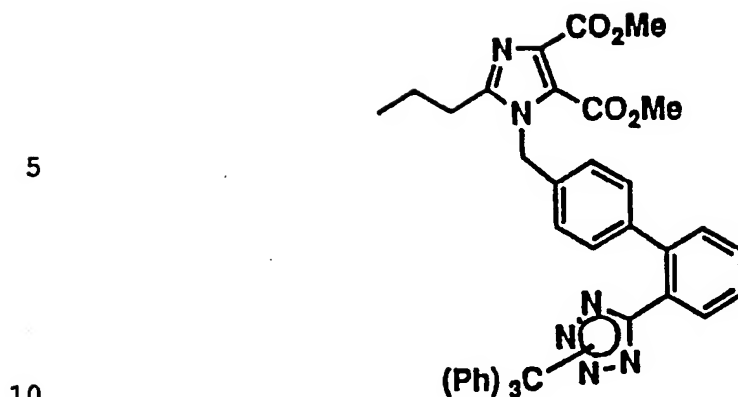
PART D: Preparation of 4,5-dicarbomethoxy-2-n-propyl-
           1-[(2'-(N-triphenylmethyl-(1H-tetrazol-5-yl))
           biphenyl-4-yl)methyl]imidazole

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        Sodium hydride (1.06 g, 44.2 mmol, 1 eq) was added
   to a solution of 4,5-dicarbomethoxy-2-n-propylimidazole
   (10.00 g, 44.2 mmol, 1 eq) in DMF at room temperature.
20 Foaming and gas evolution occurred. The temperature was
   increased to 60°C for 15 minutes to dissolve all of the
   sodium hydride. Gas evolution ceased and the mixture
   was cooled to room temperature. To this mixture was
   added a DMF solution of 2'(N-triphenylmethyl-(1H-
25 tetrazol-5-yl))biphenyl-4-yl)methylbromide (24.64 g,
   44.2 mmol, 1 eq). After 24 h, the solvent was removed
   in vacuo, and the residue was flash chromatographed in
   75:25 hexane/ethyl acetate to 100% ethyl acetate over
   silica gel to yield 25.78 g (51%) of a white glass which
30 was suitable for further transformation.
   Recrystallization from ethanol yielded an analytical
   sample (white crystals); mp: 124.0-125.5°C. NMR
   (CDCl$_3$) δ 7.91 (d of d, 1H, J=3.9 Hz); 7.59-7.20 (m,
   12H); 7.09 (d, 2H, J=9 Hz); 6.94 (m, 6H); 6.76 (d, 2H,
35 J=9 Hz); 5.30 (s, 2H); 3.89 (s, 3H); 2.50 (t, 2H, J=7

Hz); 1.67 (t of t, 2H, J=7,7 Hz); 0.85 9t, 3H, J=8 Hz).
IR (neat) 1718cm^{-1}. Anal calcd. for $C_{43}H_{38}N_6O_4$: C,
73.49; H, 5.45; N, 11.96. Found: C, 73.23; H, 5.48; N,
12.22.

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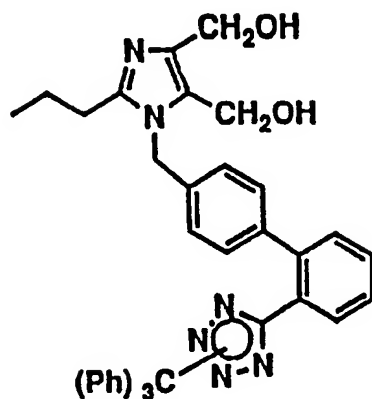
20 PART E: Preparation of 4,5-dihydroxymethyl-2-n-propyl-
             1-[(2'-(N-triphenylmethyl-(1H-tetrazol-5-yl))
             biphenyl-4-yl)methyl]imidazole

             4,5-Dicarbomethoxy-2-n-propyl-1-[(2'-(N-triphenyl-
25 methyl-(1H-tetrazol-5-yl))biphenyl-4-yl)methyl]imidazole
     (9.88 g, 14.1 mmol, 1 eq) was dissolved in a minimum of
     THF and to this solution, lithium aluminum hydride (1.0
     M in THF) (15.48 mL, 15.48 mmol, 1.1 eq) was slowly
     added dropwise. The mixture was allowed to stir at room
30 temperature overnight after which it was quenched by the
     Steinhardt procedure (Fieser & Fieser V.1, p. 584) as
     follows: to the reaction mixture water (0.66 mL) was
     first carefully added followed by 15% NaOH (0.66 mL)
     followed by water (1.97 mL). After stirring for 72 h, a
35 very fine suspension of particulate had formed which was

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slowly filtered through Celit ™. The filtrate was dried
(MgSO$_4$) and the solvent removed in vacuo to yield 8.83 g
of a yellow glass which could not be recrystallized.
This intermediate was suitable for further
5   transformation. NMR (DMSO-d$_6$) δ 7.82 (d, 1H, J=9 Hz);
      7.68-7.28 (m, 12H); 7.05 (d, 2H, J=9 Hz); 6.87 (d, 6H,
      J=9 Hz); 5.16 (s, 2H); 4.94 (t, 1H, J=7 Hz); 4.66 (t,
      1H, J=7 Hz); 4.37 (d, 2H, J=7 Hz); 4.32 (d, 2H, J=7 Hz);
      2.34 (t, 2H, J=7 Hz); 1.52 (t of q, 2H, J=7,7 Hz); 0.77
10   (t, 3H, J=7 Hz). IR (neat) 3300 br; 3061; 1027; 1006;
      909; 732; 699 cm^{-1}. Anal. calcd. for C$_{41}$H$_{38}$N$_6$O$_2$•H$_2$O: C,
      74.07; H, 6.06; N, 12.64. Found C, 74.06; H, 5.95; N,
      11.86.
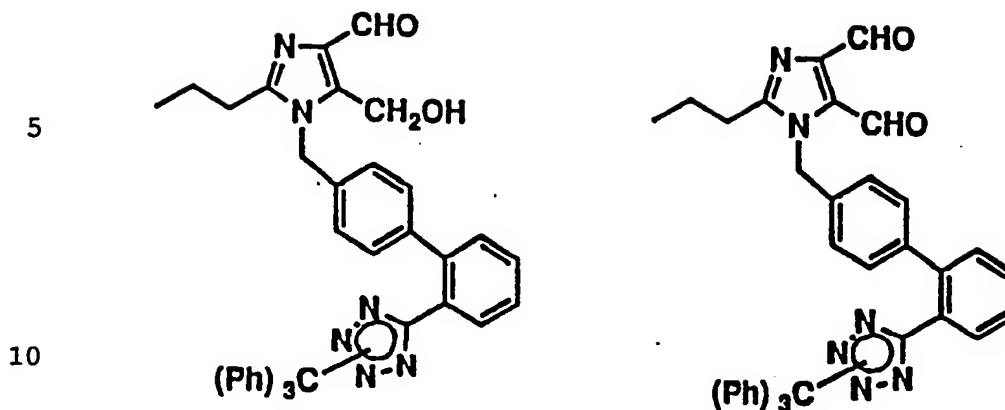
PART F: Preparation of 5-hydroxymethyl-2-n-propyl-1-
             [(2'-(N-triphenylmethyl-(1H-tetrazol-5-yl))-
             biphenyl-4-yl)methyl]imidazole-4-carboxal-
             dehyde and 2-n-propyl-1-[(2'-(N-triphenyl-
             methyl-(1H-tetrazol-5-yl))biphenyl-4-yl)-
             methyl]imidazole-4,5-dicarboxaldehyde

_____

     4,5-Dihydroxymethyl-2-n-propyl-1-[(2'-(N-triphenyl-
methyl(1H-tetrazol-5-yl))biphenyl-4-yl)methyl]imidazole
(8.56 g, 13.2 mmol, 1 eq) was dissolved in a minimum of
THF and added to a slurry of manganese dioxide (11.14 g,
128.1 mmol, 9.7 eq) in THF (100 mL) at room temperature.
After 24 h, the contents were filtered through Celite™,
the cake washed with THF, and the solvent of the
filtrate removed in vacuo. The residue was flash
chromatographed in 1:1 hexane/ethyl acetate to 100%
ethyl acetate over silica gel to yield the dialdehyde
which eluted first; 1.25 g (15%) of a tan glass. NMR
(DMSO-d_6) δ 10.27 (s, 1H); 10.17 (s, 1H); 7.81 (d, 1H,
J= 7Hz); 7.68 (m, 2H); 7.50-7.23 (m, 10H); 7.09 (d, 2H,
J=9 Hz); 6.96 (d, 2H, J=9 Hz); 6.86 (m, 6H); 5.59 (s,

2H); 2.52 (t, 2H, J=7 Hz); 1.58 (t of q, 2H, J=7,7 Hz); 0.77 (t, 3H, J=7 Hz). IR (neat) 1697; 1672cm^{-1}. Anal calcd. for $C_{41}H_{34}N_6O_2$: C, 76.62; H, 5.33; N, 13.07. Found: C, 76.46; H, 5.54; N, 12.94.

5   Continued elution yielded the 4-hydroxymethyl-imidazole-5-carboxaldehyde product as a light yellow solid: mp 164.5-166.0°C. NMR (DMSO-d$_6$) δ 9.86 (s, 1H); 7.80 (d, 1H, J=9 Hz); 7.63 (t, 1H, J=9 Hz); 7.53 (t, 1H, J=7 Hz); 7.50-7.25 (m, 10H), 7.07 (d, 2H, J=9 Hz);

10   6.97-6.80 (m, 8H); 5.47 (t, 1H, J=7 Hz); 5.29 (s, 2H); 4.63 (d, 2H, J=7 Hz); 2.37 (t, 2H, J=7 Hz); 1.49 (t of q, 2H, J=7,7 Hz); 0.73 (t, 3H, J=7 Hz). IR (Nujol) 1688 cm^{-1}. Anal. calcd. for $C_{41}H_{36}N_6O_2 \bullet (H_2O)_{0.1}$: C, 76.16; H, 5.64; N, 12.84. Found: C, 76.02; H, 5.36; N, 12.84.

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PART G: Preparation of 5-hydroxymethyl-4-[cis-
           (naphth-1-yl)ethenyl]-2-n-propyl-1-[(2'-(N-
           triphenylmethyl-(1H-tetrazol-5-yl))biphenyl-4-
           yl)methyl]imidazole

_____

1-Naphthylmethyltriphenylphosphonium chloride (6.82
g, 0.0155 mol, 2 eq) was suspended in THF (50 mL) and
potassium bis(trimethylsilyl)amide (0.75 M in toluene,
20.68 mL, 0.0155 mol, 2 eq) was added dropwise thereto
at room temperature. The resultant red solution was
heated at 45°C for 0.5 hours. Afterwards, 5-hydroxy-
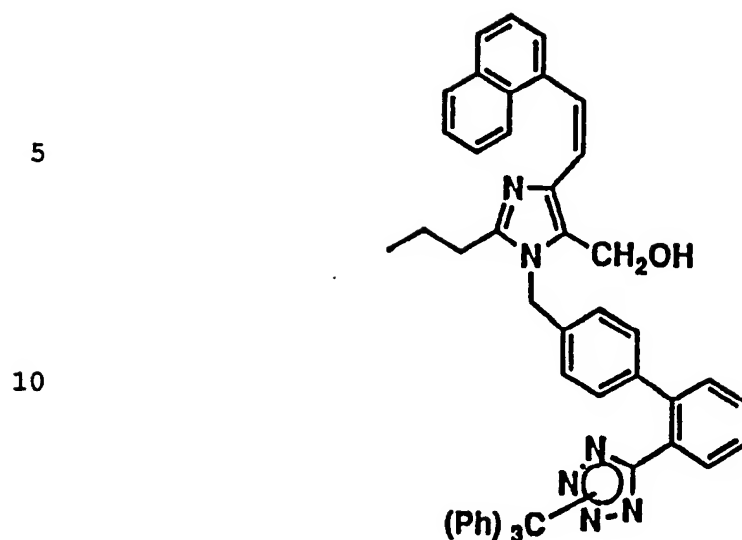methyl-2-n-propyl-1-[(2'-(N-triphenylmethyl-(1H-
tetrazol-5-yl))biphenyl-4-yl)methyl]imidazole-4-
carboxaldehyde (5.00 g, 7.75 mmol, 1 eq) dissolved in a
minimum of THF was added at room temperature and allowed
to stir overnight. The reaction was worked up by adding
300 mL of ethyl acetate and 200 mL of water. The layers
were separated and the organic layer washed with water
(2 x 200 mL). The organic layer was dried (MgSO$_4$) and

the solvent removed in vacuo to yield 9.29 g of a yellow

glass. Flash chromatography in 1:1 pentane/ethyl

acetate to 100% ethyl acetate over silica gel yielded

7.95 g of a light yellow glass. NMR (DMSO-d_6) δ

5   8.20-7.20 (m, 20H); 7.10-6.60 (m, 12H); 5.10 (s, 2H);

4.97 (t, 1H, J=7 Hz); 4.00 (m, 2H); 2.20 (t, 2H, J=7

Hz); 0.62 (t, 3H, J=7 Hz). Anal. calcd. for

$C_{52}H_{44}N_6O\bullet$(triphenylphosphineoxide)$_{1.6}\bullet$(H_2O): C, 78.76;

H, 5.73; N, 6.82. Found: C, 78.69; H. 5.67; N, 6.90.

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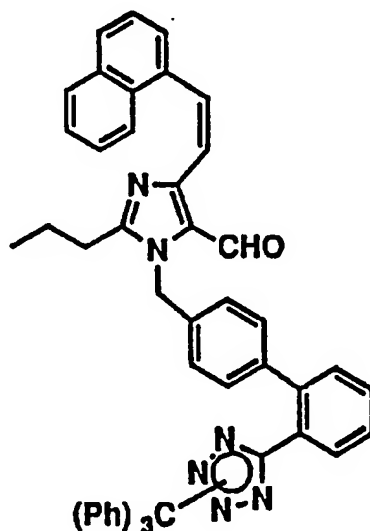
25   PART H: Preparation of 4-[cis-(naphth-1-yl)ethenyl]-
                  2-n-propyl-1-[(2'-(N-triphenylmethyl-(1H-
                  tetrazol-5-yl))biphenyl-4-yl)methyl]imidazol-
                  5-carboxaldehyde

30

        5-Hydroxymethyl-4-[cis-(naphth-1-yl)ethenyl]-2-n-
propyl-1-[(2'-(N-triphenylmethyl-(1H-tetrazol-5-
yl))biphenyl-4-yl)methyl]imidazole (7.86 g, 10.2 mmol, 1
eq), manganese dioxide (4.44 g, 51.1 mmol, 5 eq), and
35 methylene chloride (25 mL) were mixed and refluxed under

N$_2$ overnight. The manganese dioxide was filtered
through Celite™ and the cake washed with methylene
chloride. The filtrate was evaporated, and the residue
flash chromatographed in 75:25 pentane/ethyl acetate to

5   1:1 pentane/ethyl acetate to yield 3.78 g of an orange
glass. NMR (CDCl$_3$) δ 9.37 (s, 1H); 8.04 (m, 1H); 7.92
(d, 1H, J=8 Hz); 7.80 (m, 1H); 7.72 (m, 1H); 7.60-7.10
(m, 16H); 7.10-6.70 (m, 10H); 6.53 (d, 2H, J=8 Hz); 5.30
(s, 2H); 2.38 (t, 2H, J=7 Hz); 1.56 (t of q, 2H, J= 7,7

10 Hz); 0.77 (t, 3H, J=7 Hz). Anal. calcd. for
C$_{52}$H$_{42}$N$_6$O•(H$_2$O)$_{0.7}$: C, 80.12; H, 5.61; N, 10.78. Found:
C, 80.24; H, 5.91; N, 10.46.

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PART I: Preparation of 4-[cis-(naphth-1-yl)ethenyl]-
            2-n-propyl-1-[(2'-(1H-tetrazol-5-yl))biphenyl-
            4-yl)methyl]imidazole-5-carboxaldehyde

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        4-[cis-(Naphth-1-yl)ethenyl]-2-n-propyl-1-[(2'-(N-
triphenylmethyl-(1H-tetrazol-5-yl))biphenyl-4-yl)-
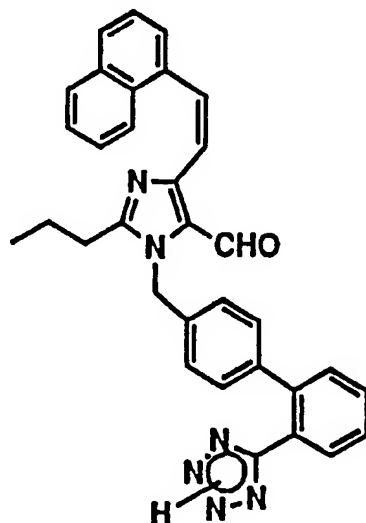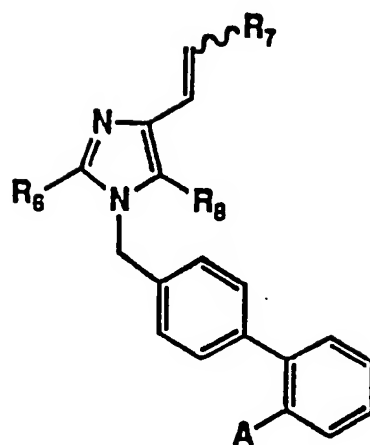methyl]imidazole-5-carboxaldehyde (3.50 g),

35 trifluoroacetic acid (12 mL), water (12 mL), and THF (40

mL) were mixed and stirred at room temperature. After 2
h, the mixture was basified with 10N NaOH to pH=12 and
the organic solvent evaporated. Water (100 mL) was then
added and a gummy solid precipitated. Ethyl ether (50
5   mL) was added and the solids dissolved. The layers were
separated and the aqueous layer extracted with ethyl
ether (2 x 50 mL). The aqueous layer was acidified with
conc. HCl to pH=2. Again gummy solids precipitated.
Ethyl acetate (100 mL) was added to dissolve these
10   solids and the layers were separated. The aqueous layer
was extracted with ethyl acetate (2 x 100 mL) and the
ethyl acetate layers were collected, dried ($MgSO_4$), and
the solvent removed in vacuo and the residue dissolved
in methanol. Water was added and the pH adjusted to 2
15   with conc. HCl. The solvent was removed in vacuo and
the residue partitioned between ethyl acetate (100 mL)
and water (100 mL). The layers were separated and the
aqueous layers extracted with ethyl acetate (2 x 100
mL). The ethyl acetate layers were collected, dried
20   ($MgSO_4$), and the solvent removed in vacuo and the
residue crystallized from ethyl acetate to yield 1.48 g
of a white solid: mp 192.5-193.5°C. NMR (DMSO-d_6) δ
9.53 (s, 1H); 8.10-7.30 (m, 1H); 7.83 (d, 1H, J=7 Hz);
7.10 (d, 1H, J=11 Hz); 7.01 (d, 2H, J=8 Hz); 6.76 (d,
25   1H, J=8 Hz); 5.46 (s, 2H); 2.42 (t, 2H, J=7 Hz); 1.34 (t
of q, 2H, J=7,7 Hz); 0.67 (t, 3H, J=7 Hz). Anal. calcd.
for $C_{33}H_{28}N_6O \cdot (H_2O)_{0.4}$:   C. 74.53; H, 5.46; N, 15.80.
Found: C, 74.48; H, 5.35; N, 15.65.

        The following compounds in Table 5 can be prepared
30   by the procedure in example 95:

Table 5
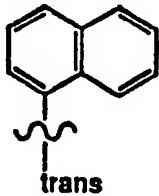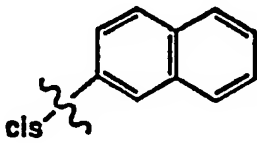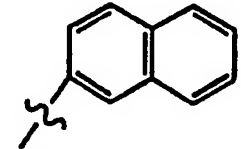
Ex. No.	R6	R7	R8	A	mp (°C)
96	n-propyl	(1-naphthyl) trans	CHO	CN4H	a
97	n-propyl	(2-naphthyl) cis	CHO	CN4H	b
98	n-propyl	(2-naphthyl) 8:3--trans:cis	CHO	CN4H	c

Table 5, continued)
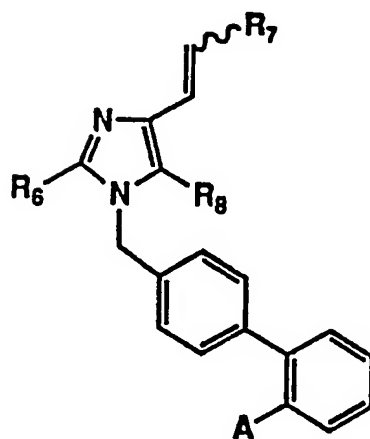
Ex. No.	R6	R7	R8	A	mp (ºC)
99	n-propyl		CH2OH	CN4H	
100	n-propyl		CHO	-NHSO2CF3	
101	n-propyl		COOH	CN4H	
102	n-propyl		CHO	COOH	

Table 5 (continued)
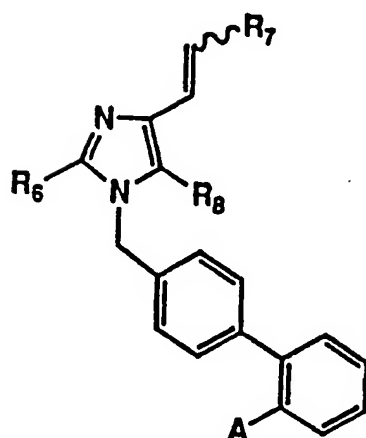
Ex. No.	R₆	R₇	R₈	A	mp (°C)
103	n-propyl		CHO	CN₄H	
104	n-propyl		CHO	CN₄H	
105	n-propyl		CH₂OH	COOH	

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Table 5 (continued)
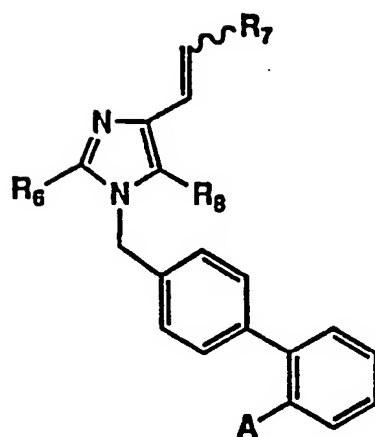
Ex. No.	R6	R7	R8	A	mp (°C)
106	n-propyl		CHO	CN4H	
107	n-butyl		CH2OH	CN4H	
108	n-butyl		COOH	CN4H	
109	n-butyl		CHO	CN4H	
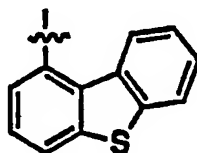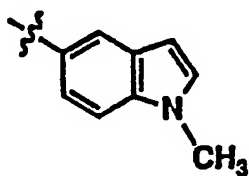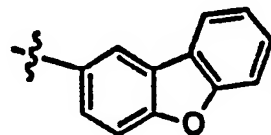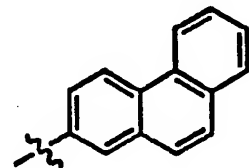
Table 5 (continued)
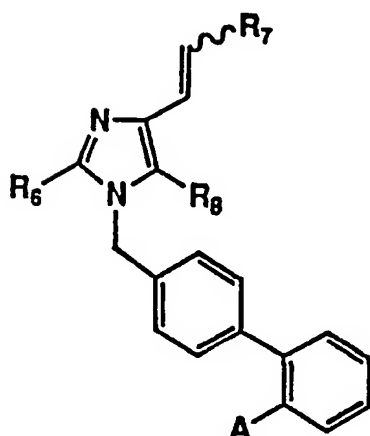
Ex. No.	R_6	R_7	R_8	A	mp (°C)
110	n-butyl		COOH	CN_4H	

[a]NMR (DMSO-d_6) ∂ 10.14 (s, 1H); 8.39 (d, 1H, J=15Hz); 8.27 (d, 1H, J=8Hz); 8.10-6.90 (m, 13H); 7.80 (d, 1H, J=15Hz); 6.87 (d, 1H, J=8Hz); 5.67 (s, 2H); 2.77 (t, 2H, J=7Hz); 1.65 (t of q, 2H, J=7,7Hz); 0.93 (t, 3H, J=7Hz).

[b]NMR (DMSO-d_6) ∂ 10.15 (s, 1H); 8.13 (s, 1H); 8.08-7.40 (m, 12H); 7.20-6.90 (m, 2H); 5.63 (s, 2H); 2.66 (t, 2H, J=7Hz); 1.64 (t of q, 2H, J=7,7Hz); 0.90 (t, 3H, J=7Hz).

[c]NMR (DMSO-d_6) ∂ (major isomer only) 9.73 (s, 1H); 8.22 (s, 1H); 8.05-7.40 (m, 10H); 7.20-6.80 (m, 6H); 5.60 (s, 2H); 2.63 (t, 2H, J=7Hz); 1.60 (t of q, 2H, J=7,7Hz); 0.85 (t, 3H, J=7Hz).

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Examples 111-123 in Table 6 can be prepared by
nucleophilic aromatic substitution of a sulfur or
nitrogen nucleophile in place of Cl, Br, or I onto the
imidazole 4 or 5-position when there is an electron
5   withdrawing group also present on the imidazole ring.
For example, a sulfur nucleophile may displace the 4-
chloro group on 2-n-butyl-4-chloro-1-[(2'-N-
triphenylmethyl(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-
imidazole-5-carboxaldehyde (synthesized as described in
10 European Patent Application No. 89100144.8, published
7.19.89) followed by appropriate deprotection or
elaboration familiar to one skilled in the art to yield
examples 113, 115, 116, 117 and 122. Other examples are
made from the appropriate starting material. The
15 nucleophilic displacement reaction may be done in an
alcoholic solvent such as methanol or a nonhydroxylic
solvent such as DMSO or DMF with or without the presence
of a base such as sodium methoxide, depending on the
nucleophilicity of the nucleophile.

Table 6

(imidazole core structure with substituents R6, R7, R8 on the imidazole ring; N-linked to a benzyl–biphenyl group bearing substituent A)
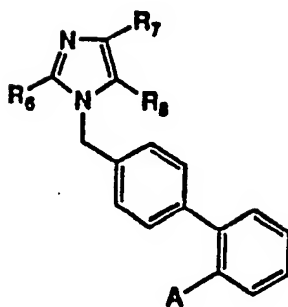
Ex. No.	R6	R7	R8	A	mp (°C)
111	n-butyl	1-naphthyl–S–	CHO	COOH	
112	n-butyl	CHO	2-naphthyl–S–	COOH	
113	n-butyl	1-naphthyl–S(=O)–	CHO	CN₄H	
114	n-butyl	2-naphthyl–S(=O)–	CHO	COOH	
115	n-butyl	anthracenyl–S–	CHO	CN₄H	

Table 6, continued
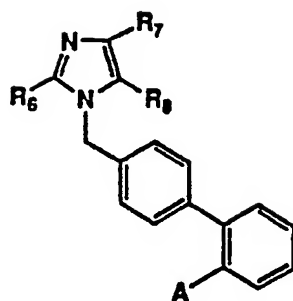
Ex. No.	R6	R7	R8	A	mp (°C)
116	n-butyl	(anthracenyl)-S-	CHO	CN4H	
117	n-propyl	(naphthalenyl)-SO2-	CHO	CN4H	
118	n-propyl	(naphthalenyl)-SO2-	NHSO2CF3	CN4H	
119	n-propyl	(quinolinyl)-S-	CHO	COOH	
120	n-propyl	(isoquinolinyl)-S-	COOH	COOH	

Table 6, continued
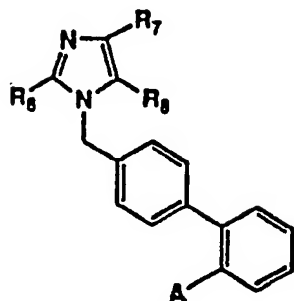
Ex. No.	R_6	R_7	R_8	A	mp (°C)
121	n-propyl		CH2OH	COOH	
122	n-propyl		CH2OH	CN4H	
123	n-propyl		CHO	COOH	

<u>Utility</u>

The hormone angiotensin II (AII) produces numerous
biological responses (e.g. vasoconstriction) through
stimulation of its receptors on cell membranes. For the
5 purpose of identifying compounds such as AII antagonists
which are capable of interacting with the AII receptor,
a ligand-receptor binding assay was utilized for the
initial screen. The assay was carried out according to
the method described by [Glossmann et al., <u>J. Biol.</u>
10 <u>Chem.</u>, <u>249</u>, 825 (1974)], but with some modifications.
The reaction mixture contained rat adrenal cortical
microsomes (source of AII receptor) in Tris buffer and 2
nM of ^{3}H-AII or 0.05 nM ^{125}I-AII with or without
potential AII antagonist. This mixture was incubated
15 for 1 hour at room temperature and the reaction was
subsequently terminated by rapid filtration and rinsing
through glass micro-fibre filter. Receptor-bound ^{3}H-AII
or ^{125}I-AII trapped in filter was quantitated by
scintillation counting. The inhibitory concentration
20 (IC$_{50}$) of potential AII antagonist which gives 50%
displacement of the total specifically bound ^{3}H-AII or
^{125}I-AII is a measure of the affinity of such compound
for the AII receptor. Compounds of this invention which
were tested in this binding assay exhibited IC$_{50}$ of
25 10^{-5}M or less (Table 7).

The potential antihypertensive effects of the
compounds of this invention may be demonstrated by
administering the compounds to awake rats made
hypertensive by ligation of the left renal artery
30 [Cangiano et al., <u>J. Pharmacol. Exp. Ther.</u>, <u>208</u>, 310
(1979)]. This procedure increases blood pressure by
increasing renin production with consequent elevation of
AII levels. Compounds are administered orally at 30
mg/kg and/or intravenously via a cannula in the jugular
35 vein at 3 mg/kg. Arterial blood pressure is

continuously measured directly through a carotid artery
cannula and recorded using a pressure transduc r and a
polygraph. Blood pressure levels after treatm nt are
compared to pretreatment levels to determine the

5   antihypertensive effects of the compounds which were
tested. Some compounds of this invention exhibited
intravenous activity at 3 mg/kg and some exhibited oral
activity at 30 mg/kg (Table 7).

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Table 7

Ex. No.	Angiotensin II Receptor Binding IC$_{50}$ (μ molar)	Antihypertensive Effects in Renal Hypertensive Rats	
		Intravenous Activity[1]	Oral Activity[2]
1	0.021	+	+
7	0.029	NA	NT
8	0.17	NA	NT
9	0.49	NA	NT
10	0.099	NA	NA
11	0.16	NA	NT
24	0.17	+	NA
41	0.11	+	+
95	0.013	+	+
96	0.56	+	NT
97	0.54	+	NT
98	0.12	+	NT

[1]   Significant decrease in blood pressure at 3.0 mg/kg or less

[2]   Significant decrease in blood pressure at 30 mg/kg or less

NA   Not active at 3 mg/kg or 30 mg/kg dosage tested.
Although some of the compounds tested were not active orally, they were active intravenously

NT   Not tested

Dosage Forms

The compounds of this invention can be administered for the treatment of hypertension according to the invention by any means that effects contact of the
5   active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration can be parenteral, i.e., subcutaneous, intravenous, intramuscular, or intra peritoneal. Alternatively, or concurrently, in some cases
10 administration can be by the oral route.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be
15 administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

For the purpose of this disclosure, a warm-blooded
20 animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency
25 of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 1-500 milligrams per day. Ordinarily, from 10 to 100 milligrams per day in one or more applications is effective to obtain desired
30 results. These dosages are the effective amounts both for treatment of hypertension and for treatment of congestive heart failure, i.e., for lowering blood pressure and for correcting the hemodynamic burden on the heart to relieve the congestion.

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The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs syrups, and suspensions. It can also be administered
5   parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed
10 tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from
15 the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.
20 In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably
25 contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents.
30 Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in
Remington's Pharmaceutical Sciences, A. Osol, a standard
reference text in this field.

Useful pharmaceutical dosage-forms for
5 administration of the compounds of this invention can be
illustrated as follows:

Capsules

A large number of unit capsules are prepared by
10 filling standard two-piece hard gelatin capsules each
with 100 milligrams of powdered active ingredient, 150
milligrams of lactose, 50 milligrams of cellulose, and 6
milligrams magnesium stearate.

15   ## Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil
such as soybean oil, cottonseed oil or olive oil is
prepared and injected by means of a positive
displacement pump into gelatin to form soft gelatin
20 capsules containing 100 milligrams of the active
ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by
25 conventional procedures so that the dosage unit is
100 milligrams of active ingredient, 0.2 milligrams of
colloidal silicon dioxide, 5 milligrams of magnesium
stearate, 275 milligrams of microcrystalline cellulose,
11 milligrams of starch and 98.8 milligrams of lactose.
30 Appropriate coatings may be applied to increase
palatability or delay absorption.

Injectable

A parenteral composition suitable for
35 administration by injection is prepared by stirring 1.5%

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by weight of active ingredient in 10% by volume
propylene glycol. The solution is made to volume with
water for injection and sterilized.

5   Suspension

     An aqueous suspension is prepared for oral
administration so that each 5 milliliters contain
100 milligrams of finely divided active ingredient, 100
milligrams of sodium carboxymethyl cellulose, 5
10   milligrams of sodium benzoate, 1.0 grams of sorbitol
solution, U.S.P., and 0.025 milliliters of vanillin.
     The same dosage forms can generally be used when
the compounds of this invention are administered
stepwise in conjunction with another therapeutic agent.
15   When the drugs are administered in physical combination,
the dosage form and administration route should be
selected for compatibility with both drugs. Suitable
dosages, dosage forms and administration routes are
illustrated in the following tables.
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Examples of NSAID's that can be combined
with AII blockers of this invention:

Drug	Dose (mg)	Formulation	Route
Indomethacin	25 (2/3 times daily)	Tablet	Oral
Meclofenamate	50-100 (2/3 times daily)	Tablet	Oral
Ibuprofen	300-400 (3/4 times daily)	Tablet	Oral
Piroxicam	10-20 (1/2 times daily)	Tablet	Oral
Sulindac	150-200 (2 times daily)	Tablet	Oral
Azapropazone	200-500 (3/4 times daily)	Tablet	Oral

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Examples of diuretics that can be combined
with AII blockers of this invention:

	Drug	Dose (mg)	Formulation	Route
5	_Drug_	_(mg)_	_Formulation_	_Route_
	Benzothiadizides (e.g. hydrochlorothiazide)	25-100 (daily)	Tablet	Oral
10	Loop diuretics (e.g. furosemide)	50-80 (daily)	Tablet	Oral

When used with an NSAID, the dosage of AII blockers
will generally be the same as when the AII blocker is
15 used alone, i.e., 1-500 milligrams per day, ordinarily
from 10 to 100 milligrams per day in one or more
applications. When used with diuretics, the initial
dose of AII blocker can be less, e.g., 1-100 milligrams
per day and for the more active compounds 1-10
20 milligrams per day.

It is expected that the compounds of this invention
will also be useful in the treatment of chronic renal
failure.

CLAIMS:

1. An antihypertensive compound of the formula:

(I)

wherein

R^1 is $-4-CO_2H$; $-4-CO_2R^9$; $-O-\overset{\displaystyle O}{\underset{\displaystyle O}{\overset{\|}{\underset{\|}{S}}}}-OH$; $-SO_3H$,

$-C(CF_3)_2OH$; $-O-\overset{\displaystyle O}{\overset{\|}{\underset{\displaystyle OH}{P}}}-OH$; $-PO_3H_2$; $-NH-\overset{\displaystyle O}{\overset{\|}{\underset{\displaystyle OH}{P}}}-OH$;

$4-NHSO_2CH_3$; $4-NHSO_2CF_3$; $-CONHOR^{12}$;

$-SO_2NH_2$; $-\overset{\displaystyle OH}{\underset{\displaystyle R^{27}}{\overset{|}{C}}}-\overset{\displaystyle O}{\underset{\displaystyle OH}{\overset{\|}{P}}}-OH$; 3-$\begin{array}{c} N-N \\ \diagup \quad \diagdown \\ \quad \quad N \\ \diagdown \quad \diagup \\ N \\ H \end{array}$;

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R^2 is H; Cl; Br; I; F; NO$_2$; CN; alkyl of 1 to 4 carbon

atoms; acyloxy of 1 to 4 carbon atoms; alkoxy of 1

to 4 carbon atoms; CO$_2$H; CO$_2$R^9; NHSO$_2$CH$_3$; NHSO$_2$CF$_3$;

$$CONHOR^{12}; \quad SO_2NH_2; \quad \text{[triazole structure]} \quad ; \quad aryl; \quad or \quad furyl;$$

R^3 is H, Cl, Br, I or F; alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

R^4 is CN, NO$_2$ or CO$_2$R^{11};

R^5 is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms;

R^6 is alkyl of 2 to 10 carbon atoms, alkenyl or alkynyl of 3 to 10 carbon atoms or the same groups substituted with F or CO$_2$R^{14}; cycloalkyl of 3 to 8 carbon atoms; cycloalkylalkyl of 4 to 10 carbon atoms; cycloalkylalkenyl or cycloalkylalkynyl of 5 to 10 carbon atoms; (CH$_2$)$_s$Z(CH$_2$)$_m$R^5 optionally substituted with F or CO$_2$R^{14}; benzyl or benzyl substituted on the phenyl ring with 1 or 2 halogens, alkoxy of 1 to 4 carbon atoms, alkyl of 1 to 4 carbon atoms or nitro;

R^7 is 1- or 2-naphthyl; 5- or 6-naphthoquinonyl; 3-, 4- or 5-acenaphthyl; 3-, 4- or 5-acenaphthenyl; 1-, 2- or 9-anthracenyl; 1- or 2-anthraquinonyl; 1-, 2-, 3-, 4-, or 9-phenanthrenyl; 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl; 2-, 3-, 4-, 5-, 6- or 7-indolyl which can be substituted on ring nitrogen with lower alkyl of 1 to 5 carbon atoms or benzyl; 4-, 5-, 6- or 7-indenyl; 2-, 3-, 4-, 5-, 6- or 7-benzofuryl; 2-, 3- , 4-, 5-, 6- or 7- benzothienyl; 1-, 2-, 3- or 4-dibenzofuryl; 1-, 2-, 3- or 4-dibenzothienyl; 1-, 2-, 3- or 4-fluorenyl; any of the foregoing polycyclic aryl groups substituted with 1 or 2 substituents selected from halogen,

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alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon
atoms, $-NO_2$, CN, $-CF_3$, $-COR^{16}$, $-CH_2OR^{17}$,
$-NHCOR^{17}$, $-CONR^{18}R^{19}$, $S(O)_rR^{17}$, and $SO_2NR^{18}R^{19}$; the
anhydride of 4, 5-dicarboxyl-1- or 2- naphthyl; or
substituted alkyl, alkenyl, or alkynyl of 1 to 10
carbon atoms substituted with a substituted or
unsubstituted polycyclic aryl group as defined
above; $-S(O)_r$-heteroaryl, $-NR^{18}$-heteroaryl, and
$-NH-SO_2$-heteroaryl;

$$R^8 \text{ is } -(CH_2)_{n-1}\overset{\displaystyle |}{\underset{\displaystyle OR^{17}}{CH}}-R^{11}; \quad -(CH_2)_n O\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{14}; \quad -(CH_2)_n SR^{15};$$

$$-CH=CH(CH_2)_s\overset{\displaystyle R^{14}}{\underset{\displaystyle |}{CH}}OR^{15}; \quad -CH=CH(CH_2)_s\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16}; \quad -\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16};$$

$$-CH=CH(CH_2)_s O\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{11}; \quad -(CH_2)_m\text{-tetrazolyl};$$

$$(CH_2)_s-\overset{\displaystyle |}{\underset{\displaystyle CH_3}{CH}}-COR^{16}; \quad -(CH_2)_n\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16}; \quad -(CH_2)_n O\overset{\displaystyle Y}{\overset{\displaystyle \|}{C}}NHR^{10};$$

$$-(CH_2)_n NR^{11}\overset{\displaystyle Y}{\overset{\displaystyle \|}{C}}OR^{10}; \quad -(CH_2)_n NR^{11}\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}NHR^{10}; \quad -(CH_2)_n NR^{11}SO_2R^{10};$$

$$-(CH_2)_n NR^{11}\overset{\displaystyle Y}{\overset{\displaystyle \|}{C}}R^{10};$$

R^9 is $-\overset{\underset{\displaystyle R^{24}}{|}}{CH}-O\overset{\underset{\displaystyle}{\overset{\displaystyle O}{\|}}}{C}R^{21}$;

R^{10} is alkyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl, 1-naphthyl, 1-(1-naphthyl)ethyl, or $(CH_2)_p C_6 H_5$;

R^{11} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{12} is H, methyl or benzyl;

R^{13} is $-CO_2H$; $-CO_2R^9$; $-CH_2CO_2H$, $-CH_2CO_2R^9$;

or $-\overset{\underset{\displaystyle}{\overset{\displaystyle O}{\|}}}{C}-NHSO_2$ $-(CH_2)_s$ —⟨benzene ring with R^{20}⟩ ;

$-O-\overset{\underset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-OH$; $-O-\overset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle O}{\|}}{P}}-OH$; $-SO_3H$; $-NH\overset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle O}{\|}}{P}}-OH$

$-PO_3H_2$; $-C(CF_3)_2OH$; $-NHSO_2CH_3$; $-NHSO_2CF_3$; $-NHCOCF_3$;

$-CONHOR^{12}$; $-SO_2NH_2$; $-\overset{\underset{\displaystyle R^{27}}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}-\overset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle O}{\|}}{P}}-OH$; ⟨tetrazole ring with R^{31}⟩ ;

$-CH_2$-⟨tetrazole ring, NH⟩ ; $-CONH$-⟨tetrazole ring, NH⟩ ; $-CONHNHSO_2CF_3$;

⟨imidazole ring with CF_3, NH⟩ ; or ⟨triazole ring with R^4, NH⟩ ;

R^{14} is H, alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{15} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl, benzyl, acyl of 1 to 4 carbon atoms, phenacyl;

R^{16} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, $(CH_2)_p C_6 H_5$, OR^{17}, or $NR^{18}R^{19}$;

R^{17} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{18} and R^{19} independently are H, alkyl of 1 to 4 carbon atoms, phenyl, benzyl, α-methylbenzyl, or taken together with the nitrogen form a ring of the formula

Q is NR^{20}, O or CH_2;

R^{20} is H, alkyl of 1-4 carbon atoms, or phenyl;

R^{21} is alkyl of 1 to 6 carbon atoms, $-NR^{22}R^{23}$,

or $-\underset{\underset{NH_2}{|}}{CH}CH_2CO_2CH_3$;

R^{22} and R^{23} independently are H, alkyl of 1 to 6 carbon atoms, benzyl, or are taken together as $(CH_2)_u$ where u is 3-6;

R^{24} is H, CH_3 or $-C_6H_5$;

R^{25} is $NR^{27}R^{28}$, OR^{28}, $NHCONH_2$, $NHCSNH_2$,

R^{26} is hydrogen, alkyl with from 1 to 6 carbon atoms, benzyl, or allyl;

R^{27} and R^{28} are independently hydrogen, alkyl with from 1 to 5 carbon atoms, or phenyl;

R^{29} and R^{30} are independently alkyl of 1-4 carbon atoms or taken together are $-(CH_2)_q-$;

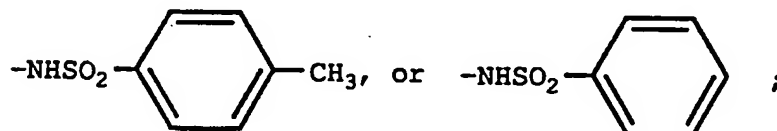R^{31} is H, alkyl of 1 to 4 carbon atoms, $-CH_2CH=CH_2$ or $-CH_2C_6H_4R^{32}$;

R^{32} is H, NO_2, NH_2, OH or OCH_3;

X is a carbon-carbon single bond, -CO-, $-CH_2-$, -O-, -S-,

$$-NH-,\ \underset{R^{26}}{-N-},\ \underset{R^{23}}{-CON-},\ \underset{R^{23}}{-NCO-},\ -OCH_2-,\ -CH_2O-,$$

$-SCH2-$, $-CH2S-$, $-NHC(R^{27})(R^{28})$, $-NR^{23}SO_2-$,

$-SO_2NR^{23}-$, $-C(R^{27})(R^{28})NH-$, $-CH=CH-$, $-CF=CF-$,

$$-CH=CF-,\ -CF=CH-,\ -CH2CH2-,\ -CF2CF2-\ ,\ \overset{\triangle}{},$$

$$\underset{-CH-}{\overset{OR^{14}}{|}}\ ,\ \underset{-CH-}{\overset{OCOR^{17}}{|}}\ ,\ \underset{-C-}{\overset{NR^{25}}{\parallel}}\ \text{or}\ \underset{-C-}{\overset{R^{29}O\ \ OR^{30}}{\diagdown\diagup}}\ ;$$

Y is O or S;

Z is O, NR^{11}, or S;

m is 1 to 5;

n is 1 to 10;

p is 0 to 3;

q is 2 to 3;

r is 0 to 2;

s is 0 to 5;

t is 0 or 1;

or a pharmaceutically acceptable salt thereof;

provided that:

(1) the R^1 group is not in the ortho position;
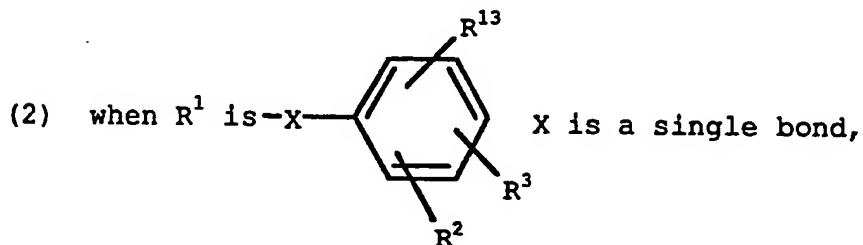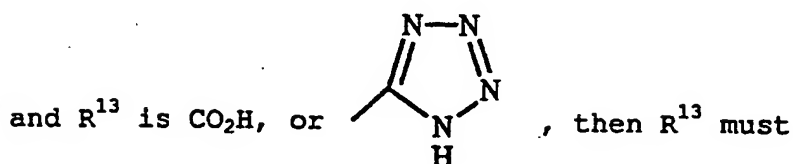
(2) when R^1 is —X— X is a single bond,

and R^{13} is CO_2H, or , then R^{13} must

be in the ortho or meta position; or when R^1 and X are as above and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, R^{13} must be ortho;

(3) when R^1 is —X— and X is other than
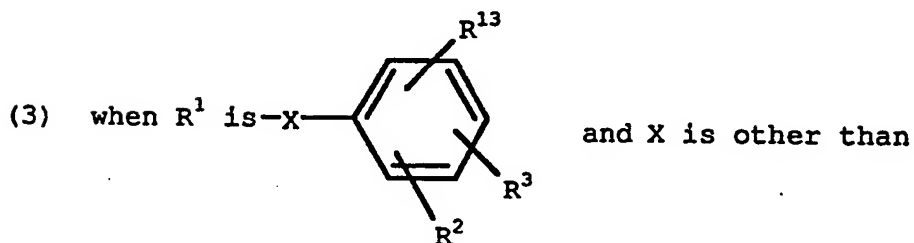
a single bond, then R^{13} must be ortho except when X = $NR^{23}CO$ and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, then R^{13} must be ortho or meta;

(4) when R^1 is 4-CO_2H or a salt thereof, R^6 cannot be S-alkyl;

(5) when R^1 is 4-CO_2H or a salt thereof, the substituent on the 4-position of the imidazole cannot be CH_2OH, CH_2OCOCH_3, or CH_2CO_2H;

CF$_3$SO$_2$HN

(6)   when R^1 is -NHCO— , R^6 is not methoxybenzyl;

(7)   the R^6 group is not -CHCH$_2$CH$_2$CH$_3$ or CH$_2$OH.
                                |
                                F

2.   A compound of Claim 1 having the formula:

(II)

wherein

R^1 is -CO$_2$H; -NHSO$_2$CF$_3$;

or

R^6 is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen, alkyl of 1 to 4 carbon atoms, and nitro;

R^8 is $-(CH_2)_m$-tetrazolyl, $-(CH_2)_nOR^{11}$; $-(CH_2)_n\overset{\displaystyle O}{\overset{\displaystyle \|}{O}}CR^{14}$;

$-CH=CH(CH_2)_s\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16}$, $-CH=CH(CH_2)_s\overset{\displaystyle R^{14}}{\overset{\displaystyle |}{C}}HOR^{15}$;

$-(CH_2)_n\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16}$; $-(CH_2)_n\overset{\displaystyle O}{\overset{\displaystyle \|}{N}}HCOR^{10}$; $-(CH_2)_nNHSO_2R^{10}$;

or $-\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}R^{16}$;

R^{13} is $-CO_2H$, $-CO_2R^9$, $NHSO_2CF_3$; SO_3H; or

R^{16} is H, alkyl of 1 to 5 carbon atoms, OR^{17}, or $NR^{18}R^{19}$;

X is carbon-carbon single bond, $-CO-$, $-\overset{\displaystyle}{\underset{\displaystyle \underset{R^{23}}{|}}{CON}}-$,

$-CH_2CH_2-$, $-\overset{\displaystyle}{\underset{\displaystyle \underset{R^{23}}{|}}{NCO}}-$, $-OCH_2-$, $-CH_2O-$, $-O-$, $-SCH_2-$,

$-CH_2S-$, $-NHCH_2-$, $-CH_2NH-$ or $-CH=CH-$;

or a pharmaceutically acceptable salt thereof.

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    3. A compound of Claim 2 wherein:

R^2 is H, alkyl of 1 to 4 carbon atoms, halogen, or
    alkoxy of 1 to 4 carbon atoms;

R^6 is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

R^7 is 1- or 2-naphthyl; 2-, 3- or 4-quinolinyl; 1-, 3-
    or 4-isoquinolinyl; or 1-, 2-, or 3-indolyl;

R^8 is $-(CH_2)_mOR^{11}$; $-(CH_2)_mO\overset{\overset{\textstyle O}{\|}}{C}R^{14}$; $-CH=CH-\overset{\overset{\textstyle R^{14}}{|}}{C}HOR^{15}$;

$-(CH_2)_m\overset{\overset{\textstyle O}{\|}}{C}R^{16}$; $-CH_2NHCOR^{10}$;

$-(CH_2)_mNHSO_2R^{10}$;   or $-COR^{16}$;

R^{10} is CF_3, alkyl of 1 to 6 carbon atoms or phenyl;

R^{11} is H, or alkyl of 1 to 4 carbon atoms;

R^{13} is CO_2H; $CO_2CH_2OCOC(CH_3)_3$; $NHSO_2CF_3$

or

;
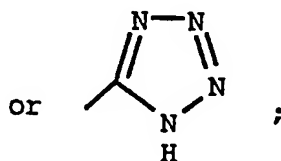
R^{14} is H, or alkyl of 1 to 4 carbon atoms;

R^{15} is H, alkyl of 1 to 4 carbon atoms, or acyl of 1 to
    4 carbon atoms;

R^{16} is H, alkyl of 1 to 5 carbon atoms; OR^{17}; or

;
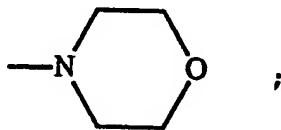
m is 1 to 5;

X = single bond, -O-; -CO-; -NHCO-; or -OCH_2-; or a
    pharmaceutically acceptable salt thereof.

4. A compound of Claim 3 wherein R^1 is
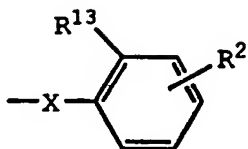
and X is a single bond, or a

pharmaceutically suitable salt thereof.

5. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a compound of any one of Claims 1 through 4.

6. Pharmaceutical composition of Claim 5 which additionally contains a diuretic or a non-steroidal antiinflammatory drug.

7. A method of preventing renal failure in a warm blooded animal resulting from administration of a non-steroidal anti-inflammatory drug (NSAID) which comprises administering, stepwise or in physical combination with the NSAID, a compound of any of Claims 1 through 4 in an amount effective to prevent renal failure.

8. A method of treating hypertension in a warm blooded animal comprising administering to the animal in an amount effective to lower the animal's blood pressure a compound of any of Claims 1 through 4.

9. Method of Claim 8 wherein a diuretic is administered to the animal prior to or simultaneously with the imidazole compound.

10. A method of treating congestive heart failure in a warm-blooded animal comprising administering to the animal a compound of any one of Claims 1 through 4 in an amount effective to correct the hemodynamic burden on the heart to relieve the congestion.

11. A process for the preparation of a compound of Claim 1 wherein r is 1 which comprises contacting an imidazole derivative of Formula 1 with a benzyl

derivative of Formula 2 in a solvent in the presence of
a base for about 1 to about 10 hours at a temperature in
the range of about 20°C to the reflux temperature of the
solvent to form a benzylimidazole of Formula 3:

5
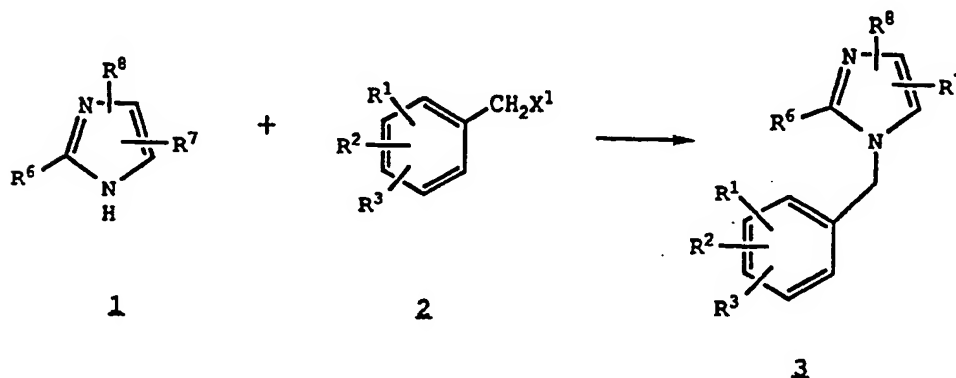
wherein each of R^1, R^2, R^3, R^6, R^7 and R^8 is stable
under the reaction conditions and is a group as defined
10   in Claim 1 or an intermediate or protected form thereof
which can be transformed to such a group and wherein X^1
is halogen, p-toluenesulfonyloxy or methylsulfonyloxy;
and thereafter as necessary transforming said
intermediate or protected forms of the R groups to R
15   groups as defined in Claim 1.

12.   Process of Claim 11 wherein compounds 1 and 2
are contacted in the presence of a base selected from
the group consisting of a metal hydride (MH), a metal
alkoxide (MOR), sodium carbonate, potassium carbonate,
20   triethylamine and pyridine, in a dipolar aprotic solvent
or, where the base is MOR, the solvent can be an
alcohol, ROH, where M is lithium, sodium or potassium
and R is methyl, ethyl or t-butyl.

13.   Process of Claim 11 wherein a two-phase
25   solvent system, one an organic phase such as methylene
chloride and the other an aqueous phase, is used in the

presenc of a phase transfer catalyst such as
tricaprylmethylammonium chloride.

14.   Process of Claim 12 wher in: R^1 is
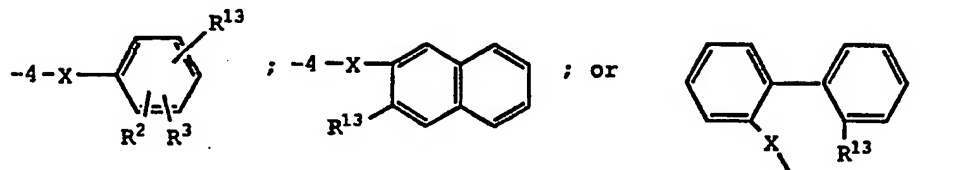
X is a carbon-carbon single bond, -CO-, -O-, -S-, or
-NH-;

R^2 and R^3 are each independently H, Cl, Br, I,
CO_2R^{14}, F, NO_2, alkyl of 1 to 4 carbon atoms,
alkoxy of 1 to 4 carbon atoms, aryl or furyl;

R^6 and R^7 are as defined in Claim 1;

R^8 is $-(CH_2)_nOR^{11}$; $-(CH_2)_nSR^{15}$; or $-(CH_2)_nCN$;

R^{11} is as defined in Claim 1;

R^{13} is CO_2R^{14}, CN, NO_2, trialkyltin tetrazole,
or trityltetrazole; and

R^{14} and R^{15} are as defined in Claim 1.

15.   Process of Claim 14 wherein R^{13} is $-CO_2R^{14}$ and
the product of Formula 3 is contacted with an alkali in
an aqueous alcoholic solvent or with CF_3CO_2H at a
temperature in the range of about 20°C to the reflux
temperature of the solvent for about 1-24 hours,
followed by adjustment of the pH of the mixture to a
value in the range of 3 to 7, to convert the product to
the corresponding product wherein R^{13} is $-CO_2H$.

16.   Process of Claim 15 wherein at least one of
R^2, R^3 or R^{13} in Formula 1 is $-CO_2R^{14}$ and is converted
to $-CO_2H$.

17.   Process of Claim 15 wherein R^{14} is t-butyl and
the reaction is conducted in CF_3CO_2H.

18.   Process of Claim 14 wherein R^{13} is -CN and the
product of Formula 3 is contacted with (i) a strong acid

at reflux temperature of the solvent for about 2-96
hours or (ii) a strong alkali in an alcohol solvent at a
temperature in the range of about 20°C and the reflux
temperature of the solvent for about 2-96 hours followed
by adjustment of the pH to about 3-7, or (iii) sulfuric
acid followed by acid or alkali, to convert the product
to the corresponding compound wherein R^{13} is $-CO_2H$.

19. Process of Claim 18 wherein at least one of
R^2, R^3 or R^{13} is $-CO_2R^{14}$ and is converted to
$-CO_2H$.

20. Process of Claim 18 wherein R^8 is $-(CH_2)_nCN$
and is converted to $-(CH_2)_nCO_2H$, or is $-(CH_2)_nOR^{11}$ and
is converted to $(CH_2)_nOH$ when R^{13} is converted to $-CO_2H$.

21. Process of Claim 14 wherein R^{13} is $-CN$ and the
product of Formula 3 is contacted with a mixture of
equimolar amounts of sodium azide and ammonium chloride
in a polar aprotic solvent at a temperature in the range
of about 30°C to the reflux temperature of the solvent,
for about 1 hour to 10 days, to convert the product to
the corresponding compound wherein R^{13} is 5-tetrazolyl.

22. Process of Claim 21 wherein R^8 is $-(CH_2)_mCN$
and is converted to $-(CH_2)_m$-tetrazolyl when R^{13} is
converted to 5-tetrazolyl.

23. Process of Claim 14 wherein R^{13} is $-CN$ and the
product of Formula 3 is reacted with trialkyltin azide
or triaryltin azide followed by acidic or basic
hydrolysis to convert the product to the corresponding
compound wherein R^{13} is 5-tetrazolyl.

24. Process of Claim 14 wherein R^{13} is $-CN$ and the
product of Formula 3 is reacted with trialkyltin azide
or triaryltin azide to produce a compound of Formula 3
wherein R^{13} is trialkyl or triaryl stannyl tetrazol-5-
yl, the latter compound is reacted with triphenylmethyl
chloride to produce a compound of Formula 3 wherein R^{13}
is triphenylmethyltetrazol-5-yl, and the latter compound

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is hydrolyzed to produce a compound of Formula $\underline{3}$ wherein R^{13} is 5-tetrazolyl.

25. Process of Claim 23 wherein R^8 is $-(CH_2)_nCN$ and is converted to $-(CH_2)_m$-tetrazolyl when R^{13} is

5 converted to 5-tetrazolyl.

26. Process of Claim 14 wherein R^{13} is $-NO_2$ and the product of Formula $\underline{3}$ is contacted with a reducing agent to form a second intermediate of Formula $\underline{3}$ in which R^{13} is NH_2, and the latter is contacted with an

10 anhydride $(CH_3SO_2)_2O$ or $(CF_3SO_2)_2O$ or a chloride CH_3SO_2Cl or CF_3SO_2Cl of sulfonic acid in a solvent to produce a compound in which R^{13} is $-NHSO_2CH_3$ or $-NHSO_2CF_3$.

27. Process of Claim 26 wherein at least one of

15 R^2, R^3, or R^{13} is $-NO_2$ and is converted to $-NHSO_2CH_3$ or $-NHSO_2CF_3$.

28. Process of Claim 15 or 18 wherein the compound of Formula $\underline{3}$ with $R^{13}=CO_2H$ either

        (a)   is contacted with about 1-4 equivalents

20 of thionyl chloride in excess thionyl chloride or another solvent at a temperature in the range of about 20°C to the reflux temperature of the solvent for a period of about 5 minutes to about 2 hours to form an intermediate of Formula $\underline{3}$ wherein R^{13} is COCl, and the

25 latter is contacted with about 2-10 equivalents of hydroxylamine derivative H_2NOR^{12} in excess hydroxylamine derivative H_2NOR^{12} or other solvent, at a temperature in the range of about 25-80°C for about 2-18 hours, or

        (b)   is contacted the hydroxylamine derivative

30 H_2NOR^{12}, dicyclohexylcarbodiimide and 1-hydroxy-benzotriazole in a solvent at a temperature in the range of about 0-30°C for about 1-24 hours; to provide a compound in which R^{13} is $CONHOR^{12}$.

29. Process of Claim 11 wherein: R^1 is
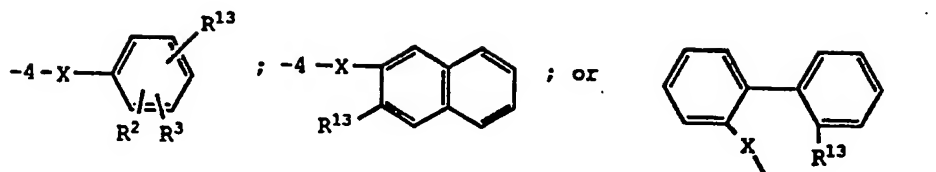
5 X is a carbon–carbon single bond, -CO-, -O-, -S-, or -NH-;

R^2, R^3, R^6 and R^7 are as defined in Claim 1; and R^8 is $(CH_2)_nOR^{11}$, $(CH_2)_nOCOR^{14}$, $(CH_2)_nCH(OH)R^{16}$, $(CH_2)_nCOR^{16}$ $(CH_2)_nCl$, $(CH_2)_nCN$, CHO.

10   30. Process of Claim 29 wherein R^8 is $(CH_2)_nOH$ and the product of Formula 3 is contacted with an alcohol $R^{11}OH$ in the anhydrous state in the presence of a strong acid or a Lewis acid, followed by saponification of any CO_2R^{14} groups concomitantly formed or present in

15 intermediate 3, to form the corresponding compound of Formula 3 wherein R^8 is $(CH_2)_nOR^{11}$ and R^{11} is not H.

      31. Process of Claim 29 wherein R^8 is $(CH_2)_nOR^{11}$ and R^{11} is not H and the product of Formula 3 is contacted with an aqueous acidic medium at a temperature

20 in the range of about 25°C and the reflux temperature of the solvent for a period of about 0.5-24 hours to form the corresponding compound of Formula 3 wherein R^8 is $(CH_2)_nOH$.

      32. Process of Claim 29 wherein R^8 is $(CH_2)_nOH$ and

25 the product of Formula 3 is contacted with

            (a) a carboxylic acid anhydride $(R^{14}CO)_2O$ or chloride $R^{14}COCl$ in a solvent in presence of a base at a temperature in the range of about 0°C and the reflux temperature of the solvent for about 0.5-24 hours or

30   (b) a carboxylic acid $R^{14}CO_2H$ under anhydrous conditions in presence of a strong acid or Lewis acid at

about 0°–100°C for about 0.5 to 24 hours, to form the
corresponding compound in which R^8 is $(CH_2)_nOCOR^{14}$.

33.   Process of Claim 29 wherein R^8 is $(CH_2)_nOCOR^{14}$
and the product of Formula 3 is contacted with aqueous

5   acid or alkali to form the corresponding compound
wherein R^8 is $(CH_2)_nOH$.

34.   Process of Claim 29 wherein R^8 is $(CH_2)_nOH$ and
the product of Formula 3 is contacted with an oxidizing
agent at a temperature of about 25–45°C for about 1–200

10   hours to produce a corresponding compound of Formula 3
in which R^8 is $(CH_2)_{n-1}COR^{16}$ and R^{16} is H.

35.   Process of Claim 29 wherein R^8 is
$(CH_2)_nCOR^{16}$ and R^{16} is H and the product of Formula 3 is
contacted with an organometallic compound $R^{16}P$ in which

15   P is MgBr or Li in a solvent at a temperature in the
range of about –78°C to 100°C for about 0.5–24 hours to
form a compound of Formula 3 in which R^8 is
$(CH_2)_nCH(OH)R^{16}$ and R^{16} is not H.

36.   Process of Claim 29 wherein R^8 is

20   $(CH_2)_nCH(OH)R^{16}$ and R^{16} is not H and the product of
Formula 3 is contacted with an oxidizing agent in a
solvent to form a corresponding compound of Formula 3 in
which R^8 is $(CH_2)_nCOR^{16}$ and R^{16} is not H.

37.   Process of Claim 29 wherein R^8 is $(CH_2)_nCOR^{16}$

25   and R^{16} is H and the compound of Formula 3 is contacted
with an oxidizing agent in a solvent to form a
corresponding compound of Formula 3 in which R^8 is
$(CH_2)_nCOR^{16}$ and R^{16} is OH.

38.   Process of Claim 29 wherein R^8 is $(CH_2)_nCOR^{16}$

30   and R^{16} is OH and the compound of Formula 3 is contacted
with thionyl chloride in excess or in another solvent at
a temperature in the range of about 0°C to the reflux
temperature of the solvent for about 5 minutes to about
24 hours to form a corresponding compound of Formula 3

35   in which R^8 is $(CH_2)_nCOCl$ followed by contact of the

latter with an amine $NHR^{18}R^{19}$ in excess or in a solvent
at temperatures in the range of about 0°C and reflux
temperature of the solvent for about 5 minutes to about
24 hours to form a corresponding compound of Formula 3
5 in which R^8 is $(CH_2)_nCONR^{18}R^{19}$.

39. Process of Claim 29 wherein R^8 is $(CH_2)_nOR^{11}$
and R^{11} is H and the product of Formula 3 is contacted
with thionyl chloride in excess or in a solvent at a
temperature in the range of about 20°C to the reflux
10 temperature of the solvent for about 0.5-24 hours to
form an intermediate compound of Formula 3 in which R^8
is $(CH_2)_nCl$.

40. Process of Claim 39 wherein the compound of
Formula 3 in which R^8 is $(CH_2)_nCl$ is contacted with
15 sodium or potassium salt of a mercaptan $R^{15}SH$ in a
solvent at a temperature in the range of about 25-100°C
for about 1-24 hours to form a compound of Formula 3 in
which R^8 is $(CH_2)_nSR^{15}$.

41. Process of Claim 29 wherein the compound of
20 Formula 3 in which R_8 is $(CH_2)_nCl$ is contacted with an
alkali metal cyanide in a solvent at a temperature in
the range of about 20-100°C for about 1-24 hours to form
a compound of Formula 3 in which R^8 is $(CH_2)_nCN$ and the
latter compound is hydrolyzed to the corresponding
25 compound of Formula 3 in which R^8 is $(CH_2)_nCOR^{16}$ and R^{16}
is OH.

42. Process of Claim 29 wherein the compound of
Formula 3 in which R^8 is $(CH_2)_{n-1}Cl$ is contacted with
the sodium or potassium salt of a dialkyl malonate in a
30 solvent at a temperature in the range of about 20-100°C
for about 0.5-24 hours to form a compound of Formula 3
in which R^8 is $(CH_2)_{n-1}CH(CO_2alkyl)_2$ followed by
saponification of the latter with aqueous alkali at a
temperature in the range of about 25°C to the reflux
35 temperature of the solvent followed by acidification

with mineral acid to form a compound of Formula $\underline{3}$ in which R^8 is $(CH_2)_{n-1}CH(CO_2H)_2$ followed by h ating the latter to about 120°C or in dilute mineral acid at reflux temperature to form a product of Formula $\underline{3}$ in

5   which R^8 is $(CH_2)_nCOR^{16}$ and R^{16} is OH.

43. Process of Claim 29 wherein R^8 is -CHO and the compound of Formula $\underline{3}$ is contacted with a methylene phosphorane $(C_6H_5)_3P=CH(CH_2)_sCHR^{14}OR^{15}$ or $(C_6H_5)_3P=CH(CH_2)_sCOR^{16}$ in a solvent at a temperature in

10   the range of about 25°C to the reflux temperature of the solvent for about 1-24 hours to form a compound of Formula $\underline{3}$ in which R^8 is $-CH=CH(CH_2)_sCHR^{14}OR^{15}$ or $-CH=CH(CH_2)_sCOR^{16}$, except where R^{15} is H and R^{16} is OH, and optionally then contacting the compound of Formula $\underline{3}$

15   in which R^8 is $-CH=CH(CH_2)_sCOR^{16}$ with a reducing agent in a solvent at a temperature of about 0°-25°C for about. 0.5-24 hours to form a product of Formula $\underline{3}$ in which R^8 is $-CH=CH(CH_2)_sCHR^{14}OH$.

44. Process of Claim 29 wherein R^8 is $(CH_2)_nOH$ and

20   the compound of Formula $\underline{3}$ is contacted with an isocyanate of Formula $R^{10}NCO$ in a solvent at a temperature in the range of about 25°C to the reflux temperature of the solvent for a period of about 5 minutes to about 24 hours to form a compound of Formula

25     $\underline{3}$ in which R^8 is $(CH_2)_nOCONHR^{10}$.

45. Process of Claim 29 wherein the compound in which R^8 is $(CH_2)_nCl$ is contacted with an amine $R^{11}NH_2$ in excess amine or another solvent for a period of about 1-24 hours at a temperature in the range of about 0°C to

30   the reflux temperature of the solvent to form an intermediate of Formula $\underline{3}$ in which R^8 is $(CH_2)_nNHR^{11}$.
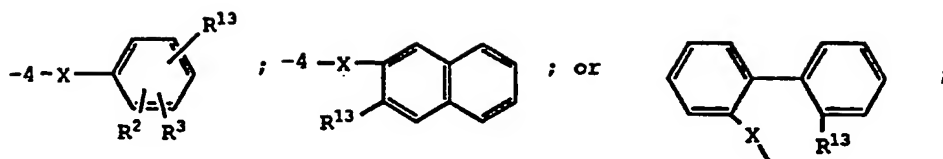
46. Process of Claim 29 in which R^8 is $(CH_2)_nCl$ and the compound of Formula $\underline{3}$ is contacted with an alkali metal azide in an aprotic solvent at a

35   temperature in the range of about 25-80°C for about 1-24

hours to form a compound of Formula $\underline{3}$ in which R^8 is
$(CH_2)_nN_3$ and the latter is contacted with a reducing
agent to form an intermediate of Formula $\underline{3}$ in which R^8
is $(CH_2)_nNH_2$.

5   47.   Process of Claim 45 or 46 in which R^8 is
$(CH_2)_nNHR^{11}$ or $(CH_2)_nNH_2$ and the compound of Formula $\underline{3}$
is contacted with a chloroformate of Formula $R^{10}OCOCl$ or
a sulfonyl derivative of Formula $R^{10}SO_2Cl$, or $(R^{10}SO_2)_2O$
in a solvent in the presence of a base at a temperature
10   in the range of about 0°C to the reflux temperature of a
solvent for about 5 minutes to about 24 hours to form a
compound of Formula $\underline{3}$ in which R^8 is $-(CH_2)_nNR^{11}CO_2R^{10}$
or $-(CH_2)_nNR^{11}SO_2R^{10}$.

        48.   Process of Claim 45 or 46 in which the
15   compound of Formula $\underline{3}$ with R^8 equal to $-(CH_2)_nNHR^{11}$ or
$(CH_2)_nNH_2$ is contacted with an isocyanate or
isothiocyanate $R^{10}NCY$ in a solvent at a temperature in
the range of about 25°C to the reflux temperature of the
solvent for about 5 minutes to about 24 hours to form a
20   compound of the Formula $\underline{3}$ in which R^8 is
$-(CH_2)_nNR^{11}CYNHR^{10}$.

        49.   Process of Claim 11 wherein R^1 is NO_2 and R^2,
R^3, R^6, R^7, and R^8 are as defined in Claim 34 in which
the compound of Formula $\underline{3}$ wherein R^1 is NO_2 is reduced
25   by means of iron and acetic acid, stannous chloride, or
hydrogen and palladium to a compound of Formula $\underline{3}$
wherein R^1 is NH_2 and the latter is reacted with an
appropriate acid anhydride such as phthalic anhydride or
a substituted phthalic anhydride in a solvent or with an
30   appropriate acid chloride such as substituted
anthranilic acid chloride in the presence of aqueous
alkali or a base or with an appropriately substituted
phthalic or anthranilic acid in the presence of
dicyclohexylcarbodiimide in a solvent to produce a
35   compound of the Formula $\underline{3}$ in which R^1 is

-4-X-⟨ring⟩-R¹³ ; -4-X-⟨naphthalene⟩ ; or ⟨biphenyl⟩ ;
with R^2 R^3 and R^{13}; naphthalene R^{13}; biphenyl X, R^{13}
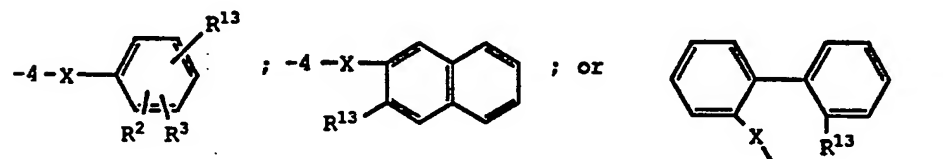
and X is NHCO.

50. Process of Claim 11 wherein R^1 is $OCH_2C_6H_5$, R^2
and R^3 are H and R^6, R^7, and R^8 are as defined in Claim
11 and the resulting compound of Formula 3 with R^1 equal
to $OCH_2C_6H_5$ is contacted with trifluoroacetic acid at
reflux temperature for a period of about 0.2–1 hour or
with hydrogen and palladium to form the corresponding
compound of Formula 3 in which R^1 is OH and the latter
is contacted with a base at about 25°C and a suitable
benzyl halide of the formula:

-Hal-CH₂-⟨ring⟩-R¹³ with R^2 R^3 ; -Hal-CH₂-⟨naphthalene⟩-R¹³ ; or ⟨biphenyl⟩ with CH_2 Hal and R^{13} ;
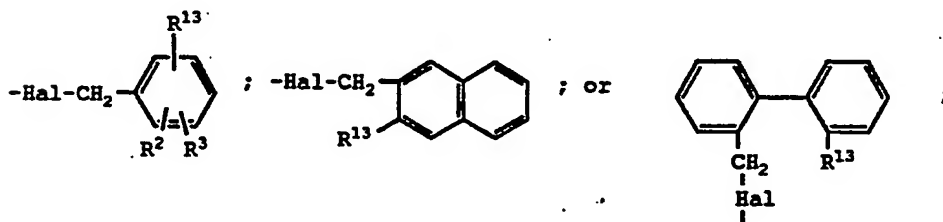
to produce the corresponding compound of Formula 3
wherein R^1 is

-4-X-⟨ring⟩-R¹³ with R^2 R^3 ; -4-X-⟨naphthalene⟩-R¹³ ; or ⟨biphenyl⟩ with X and R^{13} ;

and X is $-OCH_2-$.

51. Process of Claim 11 wherein R^8 is –CHO,
whereby the benzyl derivative of Formula 2 attaches to
the imidazole derivative of Formula 1 preferentially at

the nitrogen atom adjacent the carbon atom of the
imidazole ring to which R^8 is attached.

52. A process for th preparation of a compound of
Claim 1 wherein r is 0 which comprises contacting an
imidazole derivative of Formula 1 or its metallic salt
with 4-fluoro-1-nitrobenzene in a solvent, in the
presence of a base if the free imidazole is used, for 1-
10 days at a temperature of 25-150°C to form an N-
phenylimidazole followed by elaboration to compounds
wherein X=NHCO by the process described in Claim 49.

53. A process of Claim 29 wherein R^8 is CHO, and X
is a carbon-carbon single bond, and the product of
Formula 3 is contacted with an organometallic reagent
such as $R^{11}MgBr$ or $R^{11}Li$ in the presence of an anhydrous
nonhydroxylic solvent such as ether, THF or
dimethoxyethane at -78 to 25°C followed by aqueous work-
up followed by acid hydrolysis of any CO_2R^{14} groups
where R^{14} is t-butyl or hydrolysis of any trityl-
protected tetrazole groups to form the corresponding
compound of Forumula 3 wherein R^8 is
   $-(CH_2)_{n-1}-CH-R^{11}$, where $R^{11} \neq H$.
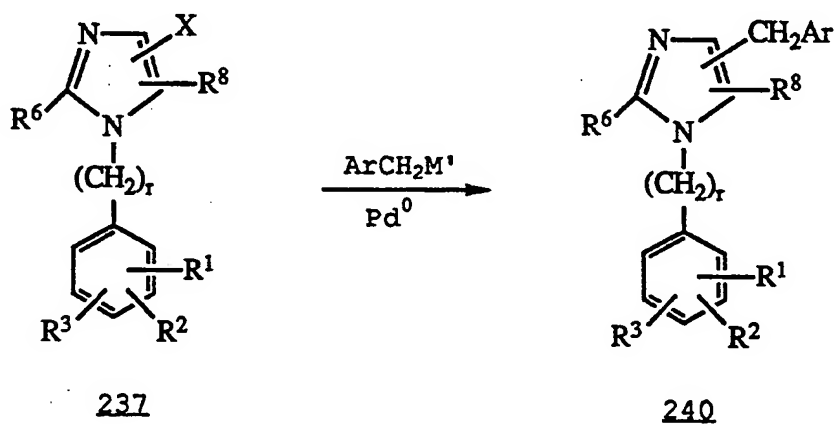 |
               OR^{17}
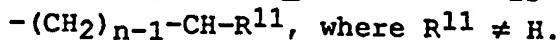
54. A process for the preparation of the compounds
of claim 1 where R^7 = aryl, heteroaryl, substituted
aryl, or substituted heteroaryl characterized in that
haloimidazole 237 is coupled with an arylmetal
derivative ArM, where M=ZnBr, Me_3Sn, $B(OH)_2$, etc. in the
presence of a transition metal catalyst such as
palladium, platinum, nickel, or zirconium, to form an
arylimidazole 238.

237   238
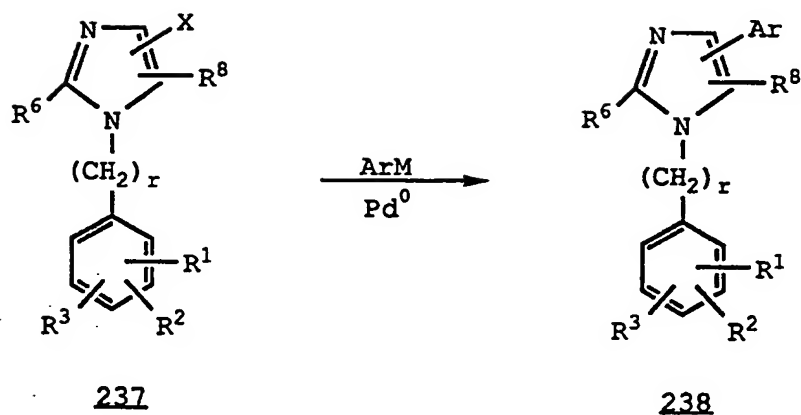
where R^1, R^2, R^3, R^6, R^8 and r have the meanings
given in Claim 1, X is Br or I, M is ZnBr, Me₃Sn,
B(OH)₂, etc., and Ar is aryl, heteroaryl,
substituted aryl, or substituted heteroaryl.

55. A process for the preparation of the compounds
of Claim 1 where R^7 = arylmethyl, heteroarylmethyl,
substituted arylmethyl, or substituted heteroarylmethyl
characterized in that a haloimidazole 237 is coupled
with an arylmethylmetal derivative ArCH₂M' in the
presence of a transition metal catalyst to form an
arylmethylimidazole 240:

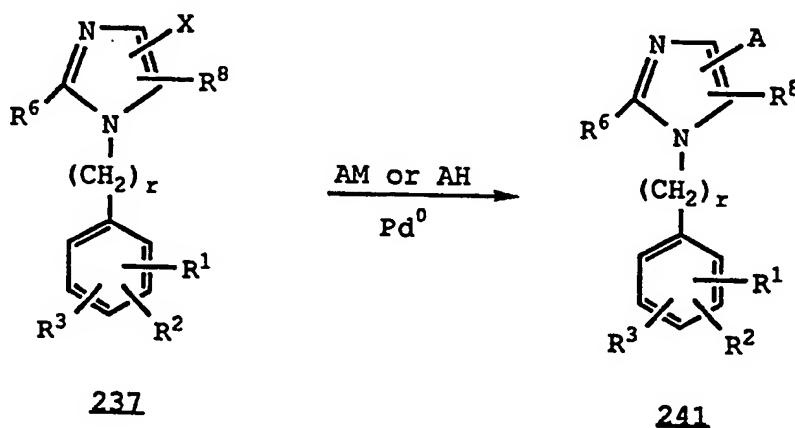

237   240

where R^1, R^2, R^3, R^6, R^8 and r have the meanings given
in Claim 1, X is Br or I, M' is ZnBr, etc., and Ar

is arylmethyl, heteroarylmethyl, substituted arylmethyl, or substituted heteroarylmethyl.

56. A process for the preparation of the compounds of Claim 1 where R^7 = substituted alkynyl or substituted alkenyl characterized in that a haloimidazole <u>237</u> is coupled with an 1-alkenylmetal or an 1-alkynylmetal derivative (AM), or an 1-alkene, or an 1-alkyne (AH) in the presence of a transition metal catalyst to form a (1-alkenyl)- or (1-alkynyl)imidazole <u>241</u>:


<u>237</u>   <u>241</u>

where R^1, R^2, R^3, R^6, R^8 and r have the meanings given in Claim 1, X is Br or I, M is a metal, A is $CH=CH(CH_2)_xAr$, or $C\equiv C(CH_2)_xAr$, Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl, and x is 0 to 8.

57. A process for the preparation of the compounds of claim 1 where R^7 = substituted alkenyl characterized in that imidazole aldehyde <u>251</u> is reacted with a substituted methylenetriphenylphosphorane to form a substituted alkenylimidazole <u>252</u>:

                 251   252
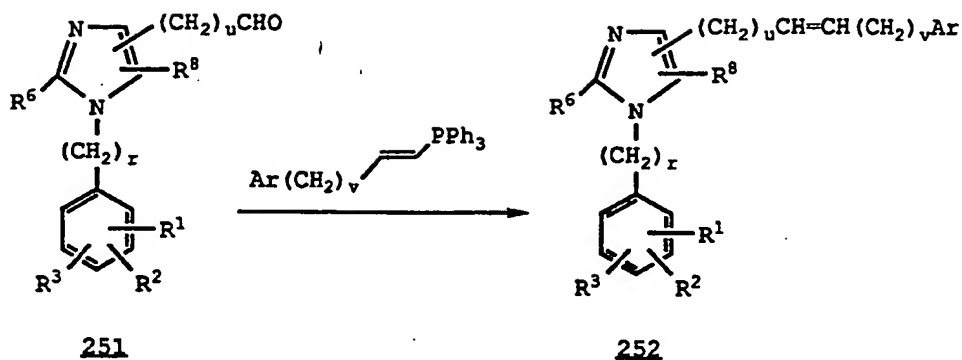
where R^1, R^2, R^3, R^6, R^8 and r have the meanings given
    in Claim 1, Ar is aryl, heteroaryl, substituted
    aryl or substituted heteroaryl, and u + v = 0 to 8.

58. A process for the preparation of the compounds
of Claim 1 where R^7 is $-S(O)_r$-heteroaryl, $-NR^{18}$-
heteroaryl, and $-NH-SO_2$-heteroaryl, characterized in
that imidazole containing compound 255 substituted with
an electron withdrawing group E are reacted with
nucleophiles in a suitable solvent at room temperature
to the reflux temperature of the solvent to result in an
aromatic substitution reaction where the leaving group X
is substituted by a nucleophile Nu such as sulfur or
nitrogen resulting in compounds of structure 256:

            255   256